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THE INFLUENCE OF DIETETIC AND OTHER FACTORS ON THE SWELLING OF TISSUES IN ARTHRITIS *

PRELIMINARY REPORT

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IN 1927 Peirce and Pemberton [15] reported data indicating that, following a stab of the finger, fewer red cells per cubic millimeter are found in the first several drops of blood of patients with severe arthritis, as compared with subsequent drops. While this difference is sometimes discovered in normal persons and in patients with mild arthritis, it is less frequent. Several possible explanations of this phenomenon have been advanced: namely, that the capillaries of normal persons are open in larger numbers; that the first issuing blood in arthritic patients is diluted in the vessels; and, that the normal or decreased number of cells in the vessels is scattered and dispersed through increased or normal amounts of serous fluids from the tissues as they issue forth.

Investigating the last mentioned possibility, Peirce, Wright and Pemberton attempted to determine the rapidity with which normal salt solution injected intradermally in the arthritic patient would be absorbed as compared with normal persons (not yet reported). McClure and Aldrich have shown that in the presence of edema there may be such an apparent avidity of the tissues for fluid that normal salt solution injected intradermally is dissipated more rapidly. The results of these experiments, however, were not sufficiently clear-cut to permit of precise evaluation, and further observations are pending. The general problem involved, however, has been brought to the fore again by other considerations which will be briefly discussed.

In a recent publication Pemberton, Peirce and Bach [14] have adduced evidence indicative of the prompt subsidence of the inflammatory or swollen tissues of the arthritic following dietetic control in suitably selected cases. They stated that a response of this nature is probably to be observed more

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promptly under these circumstances than following any other line of therapy, with the possible exception of convalescence following the removal of focal infection in very early sthenic cases. Changes may be observed as early as 24 hours following the institution of dietetic therapy and may become very graphic at the end of three or four days. This has also been previously stressed elsewhere by Pemberton.[8]

In conjunction with his associates, one of the writers has published a considerable series of studies indicating that various physiological disturbances accompany or characterize arthritis, and the American Committee for the Control of Rheumatism has expressed itself as believing that arthritis in general is a systemic disease with joint manifestations. Furthermore, in many cases of arthritis the phenomena within and around the joints are almost negligible, being greatly overshadowed by such clinical states, with the involvement of other tissues, as come under the head of myositis, neuritis, disease of the uveal tract, mental hebetude, fatigue, neurasthenia and even psychoses.

Another matter requires mention at this point. Pemberton [9] has recently pointed out that the classical syndrome of arthritis may be regarded as characterized by imbalance of at least three of the major systems of the body, viz.: the circulatory, nervous and gastrointestinal. Several lines of observation, at the hands of a number of students of arthritis, justify this conclusion. (Wright, Pemberton [19] on peripheral circulatory changes; Fletcher and Graham [3] and Pemberton and collaborators on gastrointestinal disturbances [8, 13, 14]; Rowntree, Adson [16] on nervous system dysfunctions.)

Clinical appreciation of some phases of this conception has long found expression in the views of Goldthwaite, Osgood, Swaim and their collaborators as to a probable "pooling" of blood in the arthritic, at least of the atrophic type. On the basis of this and other considerations these workers have advocated various postural attitudes and exercises which are accepted as having important clinical consequences. Sparks and Haden have also recently observed an increased blood volume in atrophic arthritis.[17]

We have been impressed with the importance of systemic rest in the therapy of arthritis, and we now regard rest in recumbency not in the vague sense of avoidance of overactivity or fatigue, but in a specific sense as contributory to changes in the gravitational influences. These are most easily appreciated in connection with the dynamics of the circulatory system, including particularly the capillary beds, but also have an equally important bearing upon the gastrointestinal and, at least clinically, upon the nervous system as well. It may be remarked, parenthetically, that in the course of observations upon soldiers in service, Pemberton [10] showed that the arthritic, as compared with the normal under similar conditions, presents a very slight lag in the elimination of water, nitrogen and particularly salt when subjected to the so-called nephritic test meal.

In planning the experiments here reported, it was decided therefore to include also observations upon patients admitted to the hospital and at once

given complete rest, since in properly selected cases the subsidence of swelling referred to above can be early detected under these circumstances.

Viewing a series of these patients undergoing successful therapy especially along nutritional lines, and having the above several considerations in mind, several clinical phenomena are to be observed, the possible significance of which has apparently largely or wholly escaped notice. These phenomena consist first of the subsidence of supposedly inflammatory tissue along the proximal and middle phalanges of many or all fingers and of the subsidence of swelling on the dorsum of the hand, beginning on the ulnar aspect. Subsidence of the swollen tissues surrounding the shafts of the phalanges may give rise to a relative increase in prominence of articular and periarticular enlargements at the phalangeal articulations, especially in the hypertrophic type. Subsidence of the dorsal tissues of the hands, however, leads to a collapsed or " all gone " appearance which renders visible, slowly but progressively, the tendons of the metacarpus.

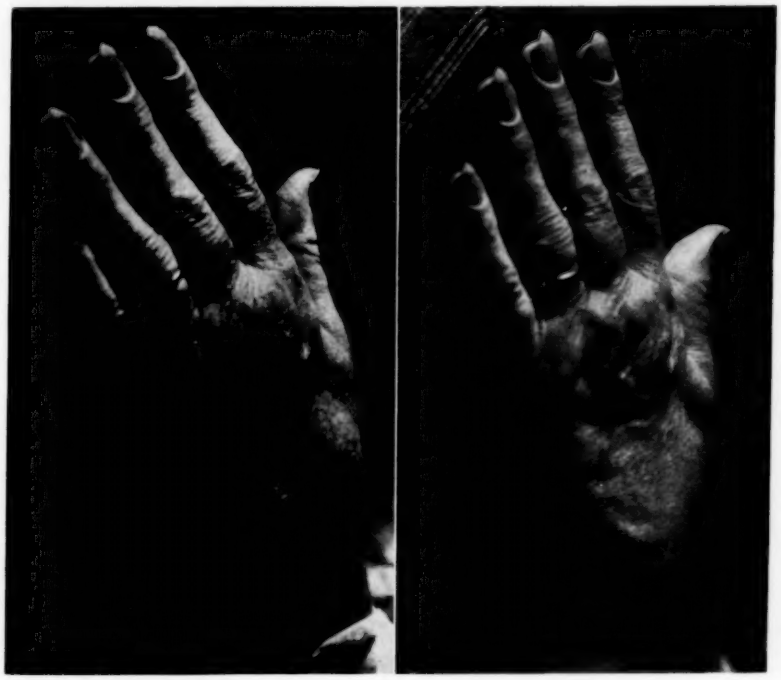


Fig. 1 Fig. 2

FIG. 1. Photograph of hand of arthritic patient before experimental period of low caloric feeding.

FIG. 2. Hand of the same arthritic patient after experimental period of low caloric feeding.

While the collapse of tissues is evident to a critical observer it is difficult to obtain striking photographic illustration of the subsidence of swelling. However, as illustrative of the type of change taking place under the

influence of dietetic measures which will be discussed later, photographs taken at the beginning and at the conclusion of an experimental period are shown in figures 1 and 2.

There takes place at the same time a progressive recession of swelling in the dorsal tissues of the hand, from the metacarpo-phalangeal articulation toward the carpus itself. At a certain stage of subsidence, the metacarpal tendons may be uncovered across the dorsum of the hand from the knuckles to a point midway between the knuckles and the wrist. The residual zone of swelling, above the hand, in turn slowly recedes upward until inspection and palpation of the hand as a whole reveal nothing but the underlying bony and tendinous structures covered by the integument itself. Conversely, exacerbations of the arthritis are accompanied by a return of swelling in the non-articular soft tissues. The process under discussion is best seen at an intermediary stage when contrasts are evident between the subsided and the unsubsided tissues. The possibility of such a subsidence on the dorsum of the hand may not suggest itself at the outset, as the hand does not necessarily or usually appear swollen. Similarly, after subsidence, nothing is obvious to suggest the previous state. Thickness and swelling, when present, of the metacarpo-phalangeal articulations likewise undergo retrogression. There is therefore a fairly close correlation between the activity of the arthritic process and the phenomenon of tissue swelling. This question is discussed in detail because it is believed that it has not been the subject of adequate scrutiny.

The nature of this swelling awaits explanation. Inasmuch as the tumefaction also concerns regions, such as the dorsum of the hand, where there are no joints, it must be regarded as something partly extraneous to the joints themselves. Furthermore, these regions are not the seat of pain such as usually characterizes the joint structures themselves in the course of arthritis. One plausible explanation is therefore that the condition under observation reflects a systemic disturbance which does not partake of an inflammatory nature in the sense usually understood by that term. The mobility of the swelling suggests further the possibility that it may represent, in part at least, an abnormal accumulation of fluids, and the observations recorded below were undertaken to determine whether such a view might be tenable. Inasmuch as satisfactory procedures for the direct quantitative estimation of fluids in the structures involved were not immediately available, recourse to an indirect method seemed necessary. As a preliminary step, observations on the approximate water balance have been made whereby gross retention or release of fluid by the body as a whole might be measured during the course of therapy primarily dietetic in nature. The recent review by Adolph [1] on water metabolism and distribution in tissues has directed attention to the possibility that some of the dietetic and other measures used in the treatment of arthritic patients may have exerted among other effects a significant influence on the distribution of water in tissues.

In view of the above considerations, studies were conducted upon the

daily water exchange in 30 arthritic patients whereby an approximate estimate of the gain or loss of fluid by the body might be obtained. The subjects were selected from among the atrophic and hypertrophic patients, admitted to the arthritis service, who seemed most likely to exhibit the above mentioned reduction of soft tissue swelling. The state of the tissues with respect to extent of swelling, pain and limitation of motion, was recorded on the basis of clinical observation, usually corroborated or checked by several persons. The method for calculating the gain or loss of water is semi-quantitative.

As indicated in table 1, the gain or loss of water is determined by subtracting the total water output from the total water intake. The water intake includes the water drunk as such and the water derived from the food. The latter factor represents the total amount of water served to the patient and the water which is produced in the body by the combustion of the carbohydrate, fat and protein in any dietary mixture. The former fraction, the water present as such in the food, is designated as preformed water; and the latter, the water produced by combustion within the body, as water of oxidation. The total water output includes the quantities eliminated through the kidney in the urine, through the bowel in the feces, through the skin and lungs in the form of sweat and water vapor.

TABLE I

Outline of Procedure for Calculation of Approximate Water Balance

Daily water exchange

Intake		*Output*	
Water as such		Urine	
Volume measured	————	Volume measured	————
Water from food		Feces	
Servings weighed		Weight (gm.) × % water	————
Composition calculated			
Preformed water	————	Skin and lung loss	
Water of oxidation	————	Estimate heat production	
Protein (gm.) × 0.413	————	H.P. (Cal.) × 0.6	————
Fat (gm.) × 1.07	————		
Carbohydrates (gm.) × 0.555	————		
TOTAL	————		————

"Approximate Water Balance" = Total Intake − Total Output

The contributory factors constituting the total water loss are more or less evident, except perhaps, the indirectly calculated estimate of the skin and lung loss. Direct determinations of the insensible losses were not made because of the fact that scales suitable for weighing patients with a sensitivity of a few grams were not available. In view of this, use was made of the empirical generalization of Benedict and Root [2] that the insensible loss

is a function of the heat production. The factor of 0.6 c.c., water lost per calorie of heat production, is taken from data presented by Adolph.[1]

The fact that the activity of the patients under observation in the present series was relatively constant from day to day is believed to justify the use of this arbitrarily determined constant. It is recognized that the approximation of water calculated according to the above procedure falls short of the more complete and more nearly accurate estimate outlined by Wiley and Newburgh [18] but as a practical expedient it seems adequate to reveal the contrasts upon which the present studies are based. In this general connection it is important to note that, with the deposition of one gram of protein or carbohydrate in the tissues, approximately three grams of water are stored. The storage of one gram of fat is associated with the deposition of one-tenth gram of water. During starvation, the tissues are of necessity broken down to supply energy for metabolism and incidentally the water bound by the substances catabolized is released. Under such circumstances there would be a net loss of water from the body. During periods of low caloric supply a negative water balance develops on the basis of the above premises. In view of these facts the food intake and the water balance are correlated with the clinical findings in the following cases.

TABLE II

Daily Water Exchange in an Atrophic Arthritic Under Conditions of Recumbent Rest, Slightly Modified Diet and Ward Care

Day of Observation	Diet			Total Calories	Total Water Intake	Total Water Output	Balance
	P.	F.	C.				
1	59	82	134	1506	1559	2150	−590
2	70	97	129	1661	2300	2810	−510
3	54	55	174	1406	1790	2460	−690
4	77	106	149	1860	2380	2398	− 18
5	69	77	136	1514	3055	2745	+310
6	88	106	169	1973	2170	2520	−350
7	60	79	243	2095	2205	2300	− 95
8	88	98	314	2470	2307	2540	−233
9	84	119	216	2271	2204	2170	+ 34
10	66	94	158	1744	2462	2665	−203
11	77	78	221	1943	2484	2260	+224
12	64	117	126	1811	2109	2780	−671
13	60	111	112	1690	1913	2055	−142

Estimated caloric requirement 1700 cal./24 hours. A progressive decrease in swelling, pain and limitation of motion occurred, the most rapid change taking place during the first few days.

In order to illustrate the general trend of the daily fluid exchange with respect to the clinical phenomenon of tissue swelling, data of a representative case of atrophic arthritis indicating an apparent systemic loss of fluid coincident with a decrease in tissue swelling, pain and limitation of motion, are presented in table 2.

Of the several possible factors contributing to the above result the influence of the inadequate caloric intake voluntarily selected from the house diet by the subject must be considered. The following three cases illustrate the uncomplicated results of the reduced caloric intake. Each of the three patients in this group made significant advances during a preliminary period in the hospital, but at the time of the experimental period had reached a state of equilibrium with residual swelling.

In table 3 (case Bkf.) are shown the findings in such a stabilized case, indicating that a sharp curtailment of calories results in a net loss of water from the body. This patient at the time of this observation had been a bed-ridden invalid for 20 months and it is possible, therefore, to discount all essential influences referable to posture, the prone position, etc. The diet consisted of orange juice, milk for breakfast and lunch, and a light, mixed but balanced, dinner. Coincident with the apparent water loss there was a reduction of tissue swelling. Like changes were observed in similar cases on correspondingly reduced food intakes.

TABLE III

Daily Water Exchange in Arthritic Cases Subjected to Low Caloric Intake

Name	Time in Bed Before Experimental Period Mo.	Diet			Calories	Water Balance	Swelling Pain
		P.	F.	C.			
Bkf.	20	47	81	121	1400	+200	
		23	37	93	800	−175	
		30	38	97	800	−175	
		44	103	98	1500	+200	Decreased
Fkln.	1	51	125	117	1800	−174	
		51	125	117	1800	− 58	
		17	16	71	500	−1050	
		17	16	71	500	−349	
		44	131	108	1800	+335	Decreased
		44	131	108	1800	+328	
Ce.	1	12	2	102	470	− 35	
		17	2	122	570	−591	
		21	11	148	675	−251	
		74	126	121	1910	+250	Reduced
		74	126	121	1910	+635	

Estimated calories required: Bkf. 1400; Fkln. 1600; Ce. 1900.

Table 3 (case Fkln.) shows the coincident reduction of swelling and net water loss under the influence of a low caloric liquid diet consisting solely of orange juice and milk. It may be noted in passing, that a negative water balance occurs even in the presence of an unrestricted supply of water, under the conditions of a so-called fluid diet which provides a submaintenance total of calories. This is obviously referable to the fact that the tissues are called upon to supply the deficit of energy and incidentally yield the water with which the protein, fat and carbohydrate are combined.

The data of these two cases serve to emphasize the fact that dietetic measures may be utilized to induce further improvement in patients who have already been given the benefit of the sum of factors involved in a régimen including recumbent rest. In each case sufficient time had elapsed before the dietetic measures were brought to bear for a more or less stable equilibrium to be attained, and it appears reasonable therefore to attribute the change noted to the reduced caloric intake uncomplicated by the physiological effects incident to postural changes. Further considerations bearing on this point will be mentioned later.

Table 3 (case Ce.) shows the effect in one patient of the vitamin-free diet, consisting of crackers, gruel, and coffee, used by Pemberton, Peirce and Bach [14] in a series of cases recently reported. This diet is not only low in vitamins but is likewise calorically inadequate. A negative phase of water balance is coincident with the period of underfeeding. While this particular patient, in whom the most evident swelling consisted of an effusion in the knee, did not exhibit a distinct decrease in tissue swelling in the sense here understood, the deduction is unavoidable that similar systemic losses of water occurred in all of the patients included in the preceding series.[14] A positive correlation of the observed rapid subsidence of tissue swelling with a negative water balance during the experimental diet periods presumably existed, therefore, in the series cited.[14]

The data presented suggest that the phenomenon of reduced tissue swelling is, under the conditions described, associated with nutritional factors involving a net loss of water from the body. The question may still be raised whether the subsidence of swelling during dietetic measures is due to (1) a physiological variation of normal tissue substance and fluids; (2) a loss of pathological cellular tissue substance; or (3) a loss of a pathological surfeit of fluid. The first factor does not appear adequate in explanation because of the fact that the swelling tends to remain subsided in the post-experimental periods following the physiological "pickup" of the bulk of the water lost.

The data available at present are insufficient to provide an adequate basis for choice between the two last mentioned possibilities, although the evidence is suggestive of the existence of a pathological surfeit of extra-cellular fluid. In further support of the view that something more than a normal physiological loss of water is involved, one experiment is cited in which an approximate estimate of the fluids released from the breakdown of normal tissues has been made.

Table 4 (Mrs. Sm.) shows data on the fluid balance in a series of observations wherein technical errors seem to be at a minimum. While it is realized that the metabolic mixture derived from tissues must contain certain quantities of carbohydrate, data on the respiratory quotient are not at hand to indicate this ratio, and it is necessary to utilize the approximation outlined below.

TABLE IV

Daily Water Exchange in a Patient Who Exhibited a Subsidence of Tissues on a Submaintenance Diet Although Stabilized with Respect to Effects of Posture

Day of Obs.	Diet			Calories	Estimated Caloric Output	Nitrogen		Tissue Loss		Water from Breakdown of Tissue	Water Bal.[1]	Water Bal.[2]
	P.	F.	C.			Intake	Output	P.	F.			
1	45	31	125	962	1350	7.2	10.3	19	35	97	−484	−387
2	44	49	89	980	1350	7.0	10.8	24	31	117	+331	+448
3	49	40	104	962	1350	7.8	11.2	21	34	112	−923	−811
4	49	37	85	869	1350	7.8	11.4	23	43	116	−542	−426
5	55	48	96	1036	1350	8.8	10.3	9	30	69	−431	−362
6	54	36	116	1008	1350	8.6	10.1	9	34	71	−190	−119

[1] Water balance calculated according to procedure outlined before.
[2] Water balance calculated according to scheme in text.

An approximation of the amount of water derived from the breakdown of cellular tissues has been made on the basis of the general premises indicated earlier as being operative during periods of submaintenance. The calorie deficit between the diet and the estimated energy output has been assumed to be made up by tissue breakdown, with corresponding release of water. It is assumed that the negative nitrogen balance measures the protein loss. The amount of calories supplied by the tissue protein subtracted from the calorie deficit is taken as representing the fat burned. On the basis of these figures the amount of water released by the breakdown of the protein and fat is calculated by considering that three grams of water are derived from one gram of protein and one-tenth gram of water from each gram of fat. By adding to the sum of those quantities the amounts of water derived by oxidation, according to the method detailed in chart 1, the total amount of water from the tissues is estimated. From this estimate it appears that extracellular tissue water contributed significantly to the net loss of water from the body under the conditions of a slightly submaintenance diet in a patient long previously stabilized with respect to the effect of posture.

If the phenomenon of reduction of swelling of tissues as here understood be related to systemic water loss, it might be expected that diets so devised as to be additionally dehydrating would induce even more marked clinical changes. Diets which approximate, in the percentage of the three foodstuffs, the endogenous metabolic mixture utilized by the body consequent upon conditions of submaintenance might therefore be useful for this purpose; that is to say, diets relatively high in protein or high in fat as compared with the ordinary high carbohydrate supply. It might be noted here that the balanced diet recommended by one of the present authors usually entails a reduction of the carbohydrate and a relative increase in the fat and protein as compared with the average dietary. From this point

of view the experimental diets here discussed may be considered as extreme variants of the type of " arthritic " diet most commonly used.

In order to illustrate the relationship of the protein and fat, several patients were accordingly placed on diets isocaloric with the preliminary diets but relatively increased in protein or fat.

Table 5 (case Shck.) shows typical findings in a subject, previously equilibrated with respect to posture, upon a diet relatively increased in protein. The diet was prepared with a minimum amount of salt and the fluid intake was restricted. An apparent loss of water occurred with the observed reduction in tissue swelling. It should be noted in passing that this patient exhibited a subsidence of tissue swelling of the type here discussed despite the fact that she presented definite and advanced hypertrophic arthritis as shown by roentgenograms of the hands and knees. There was no cardiac decompensation.

TABLE V

Approximate Water Exchange as Influenced by Qualitative Character of Diet

Patient	Day	Diet			Calories (Intake)	Calories (Output) (Calculated)	Water Balance	Swelling Pain
		P.	F.	C.				
Shck.	1	55	112	192	2000	1700	+398	
	2	46	74	84	1180	1700	(−50)	
	3	100	100	100[1]	1700	1700	−421	
	4	100	100	100[1]	1700	1700	−274	
	5	50	100	150	1700	1700	+ 52	Decreased
	6	55	95	125	1625	1700	−165	
Danr.	6	60	102	111	1774	1500	+244	
	7	80	102	114	1786	1500	−298	
	8	59	103	115	1795	1500	+162	Progressive decrease
	9	53	163	15	1735	1500	−810	
	10	53	163	15	1735	1500	+268	
	11	53	163	15	1735	1500	−214	
	12	53	163	15	1735	1500	−250	
	13	63	119	115	1782	1500	+778	
	14	60	122	116	1799	1500	+478	
	15	58	112	107	1730	1500	+ 37	

[1] Low in salt, fluid intake restricted.

It is to be further observed that two of the cases in the series here presented showed unmistakable and uncomplicated evidences of hypertrophic arthritis. In some other cases, previously seen to respond in the same way to the nutritional principles involved, the type was equally definitely hypertrophic. Two illustrative roentgen-rays are appended; one of atrophic and the other of hypertrophic arthritis (figures 3 and 4). The implication is therefore clear that both types of the disease must be regarded as presenting, in some cases at least, the phenomenon of excess tissue fluids; and also, that both types respond about equally to the same therapeutic influences discussed above.

Table 5 (case Danr.) shows the results in a case subjected to a ketogenic diet. This patient experienced a progressive decrease in swelling and pain during the period of observation. However, there was seemingly a slight acceleration in the rate of improvement during the period of increased water

Fig. 3

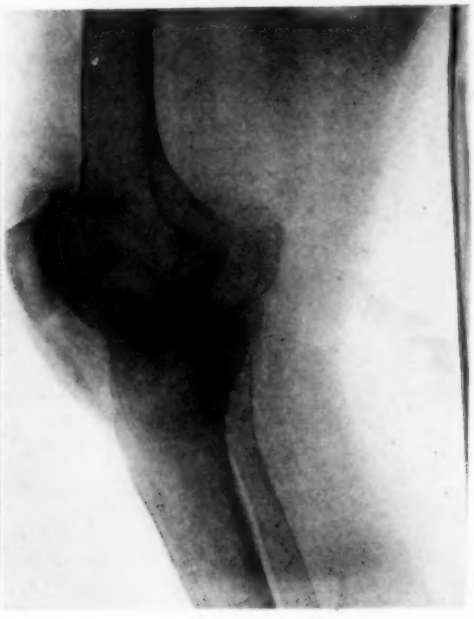


Fig. 4

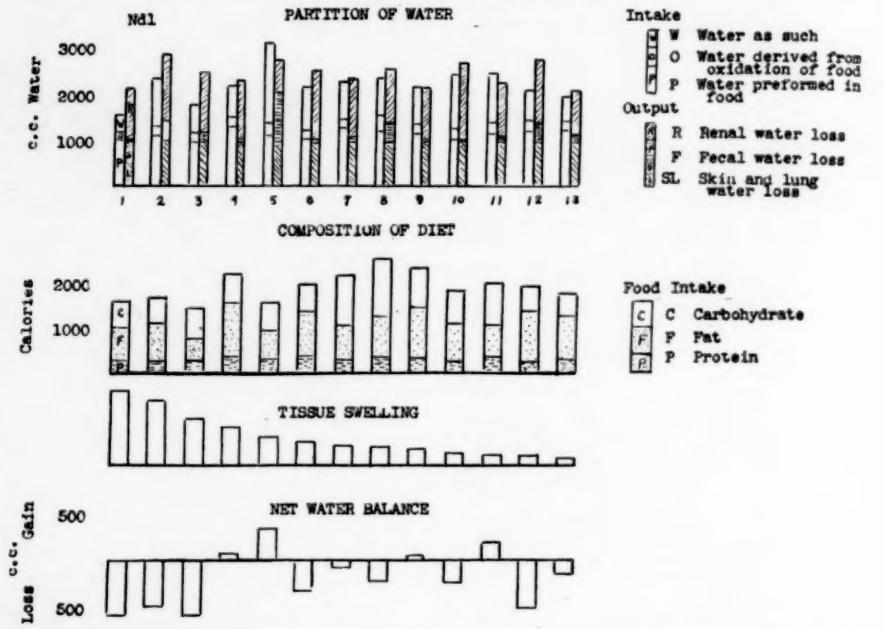
FIG. 3. Roentgenogram of hands of an atrophic arthritic patient (Bkf.).
FIG. 4. Roentgenogram of knee of a hypertrophic arthritic patient (Shck.).

loss while on the ketogenic diet. The slight acceleration in rate of recovery in this and one other case (C. Sm.) during a ketosis imposed by dietary means is not now to be considered a recommendation for the therapeutic application of such a diet. Further studies in this connection are pending.

Such observations as the above series affords again indicate the necessity for taking into account the influence of dietetic factors which may be incidental to other therapeutic measures.[8] Further evidence is thus adduced that the early onset of objective improvement from surgical procedures, such as tonsillectomy, for example, is sometimes related to the nutritional state incidently imposed rather than to the operation per se. The influence of nutritional factors is probably operative in all cases and may be conspicuous if the early clinical betterment, often experienced by patients as observed objectively, is not maintained. During or following recovery from an operation which has not removed the cause of the arthritis, the patient usually returns to a fuller dietary, and swelling and pain may then gradually return. Instances of this are legion in the experience of every close observer of arthritis.

CHART I

Daily Water Exchange in a Case of Arthritis under Conditions of Recumbent Rest, Slightly Modified Diet and Ward Care



The favorable influence exerted on the patients by recumbent rest has already been mentioned as contributory to the clinical improvement noted in patients subjected to hospital care. It has been further emphasized that the favorable effect of bed rest represents the result of many physiological and mechanical factors. The extent and nature of their interrelationships as they bear upon the problem of arthritis require more extended consideration.

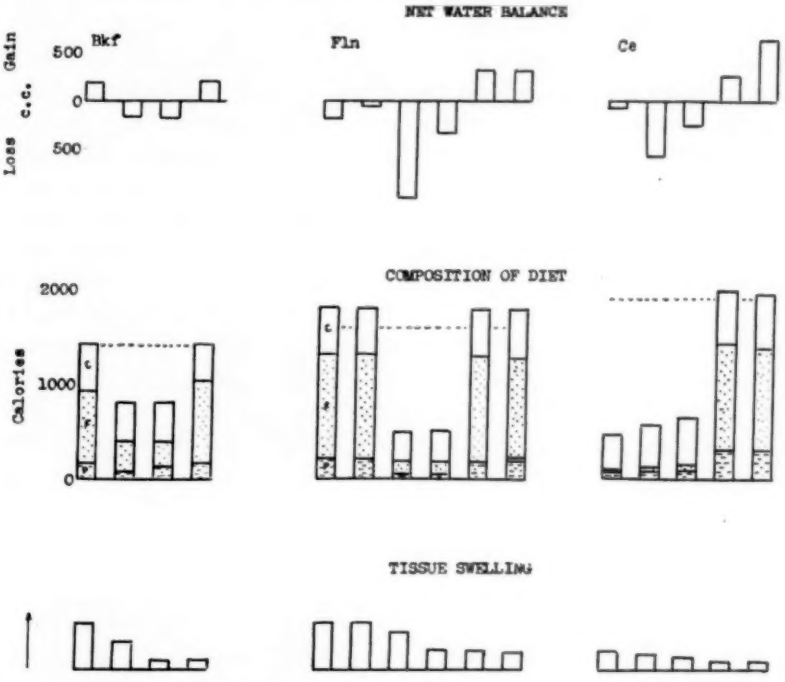
The various major systems of the body, namely, the circulatory, nervous, gastrointestinal and respiratory, are admittedly related to and interdependent upon each other. The reader need hardly be again reminded that the capillary beds in many of the tissues of the arthritic patient are more or less reduced. The normal condition of the circulation in the capillary beds of the gastrointestinal tract is probably a most important factor, but the state of the capillary beds elsewhere in the body is almost equally important in that this determines in part the distribution of the blood in the gastrointestinal tract and in various tissues where its respiratory and other functions are exercised.

Among arthritic subjects, in whom anatomical displacements and dysfunctions of the gastrointestinal tract are the rule as much as the exception, the relationships above indicated become even more significant. Inasmuch as the removal of gravitational influences achieved by the assumption of the supine rather than the erect posture profoundly alters conditions within the

circulatory system including conspicuously the capillary beds, it follows that these influences must presumably be reflected in the function of the various parts of the gastrointestinal tract as a whole. To this consideration may be added the fact, as pointed out elsewhere, that such departures from normal within the gastrointestinal tract as gastroptosis, enteroptosis and the like, with an attendant train of symptoms illustrated by hyperchlorhydria, are equally benefited by a position of recumbency in which previously operative gravitational influences are modified or removed.

CHART II

Daily Water Exchange in Arthritic Cases (Stabilized with Respect to Posture) Subjected to Low Caloric Diets



This brief recital of the influences which assumption of recumbency and betterment of the finer circulation exert upon patients, and even upon normal subjects, will suffice to indicate, as the experiments cited show, that the prescription of recumbency and a modified diet in arthritis constitutes reciprocals which cannot wholly be divorced one from the other.

Thus, under conditions characterized by gravitational handicaps it is sometimes necessary among these patients to reduce the load imposed by digestive and nutritional burdens to a minimum. Under conditions of restored gravitational equilibrium a greater nutritional and digestive burden may then often be assumed. After a certain departure from the normal is again reached, however, the nutritional and digestive burden must again be

reduced even though the favorable influence of gravitational and postural factors is at a maximum. This possibility is illustrated by three cases in the series.

It might be expected that a condition, which for the moment may be designated as excess fluid in the tissues, would be open to influence from several directions and this is indeed the case. It is therefore hardly necessary to point out the therapeutic corollary to these considerations: that the arthritic subject must be given the benefit of the several measures and influences which ameliorate the various manifestations of disturbed physiology.

One phase of the foregoing considerations relating to the effect of posture on the circulatory system may be considered in detail: the direction of the physiological transfer of fluid between the blood vessels and the tissue spaces following the assumption of various postures.

Krogh [5] and others [1] have shown that the assumption of upright posture is associated with an increased flow of fluid from the capillaries to the tissues, whereas the direction of fluid transfer may take place in the opposite direction in changing to the recumbent position. In conformity with the above, the present authors have observed changes in the specific gravity of the venous blood of arthritic patients when standing and when lying down. Average data are shown in table 6. This table indicates that there is an evident transfer of fluid to the tissues from the blood on standing and an exchange in the reverse direction on lying down. It is suggested that this mechanism contributes to the reduction of swelling when patients are placed on a régimen which includes bed rest. Studies in the writers' laboratory indicate that a sufficiently refined technic for detecting possible differences between arthritic patients and normal controls in this respect is not yet available.

TABLE VI

Relation of Posture to the Direction of Fluid Transfer, as Shown by Specific Gravity of Venous Blood; Average of Five Cases

Time (min.)	Position	Sp. Gr. Venous Blood Plasma
0	Recumbent	1.026
20	Standing	1.028
40	Recumbent	1.026
60	Standing	1.028
80	Recumbent	1.026

The suggestion is advanced on the basis of the preliminary data here presented, that the phenomenon of tissue swelling in arthritis may be regarded as one expression of the factors operative to induce other kinds of tissue swelling.

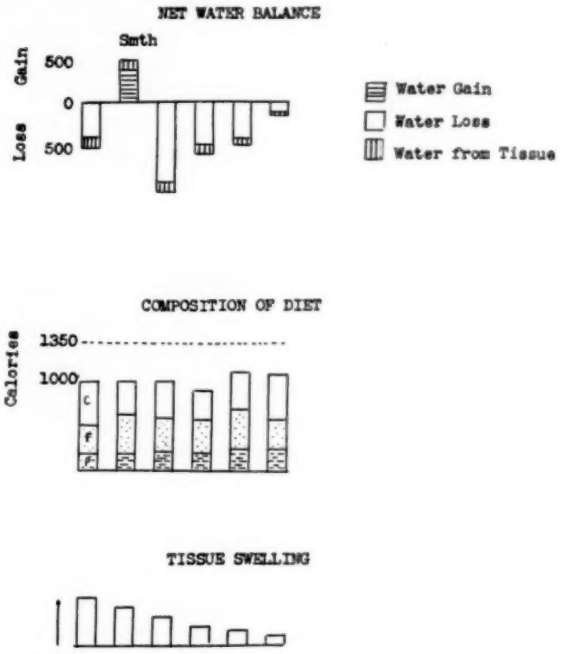
In accordance with the opinion that an abnormal fluid accumulation in the tissues contributes to the dynamic pathologic changes of arthritis, several apparently diverse factors known to exert an influence on the symptoms may be conceived as having a common basis.

The accumulation of tissue fluid may contribute to the decreased vari-

ability of the heat regulating function of the skin noted by Pemberton and Wright. The cold clammy hands of arthritics may be related to the same factor. Analogously, meteorologic changes which adversely influence symptoms may act through the lessened ability of the tissues of these patients to redistribute fluids readily. Similar considerations may apply to the decreased utilization of oxygen by the peripheral tissues [11] as well as to the delayed sugar removal.[10, 20]

CHART III

Daily Water Exchange in an Arthritic Case (Stabilized with Respect to Posture) Subjected to a Low Caloric Diet



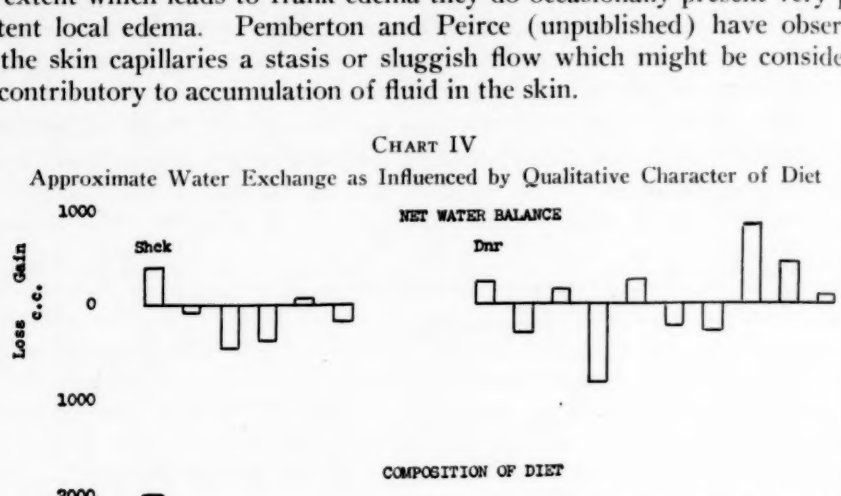
The slightly lowered basal metabolism encountered in about 33 per cent of arthritics [4, 18] may depend in part upon an accumulation of inactive tissue fluid. The observation by Sparks and Haden [17] of an increased plasma volume in atrophic arthritis further suggests that the relatively more fixed tissue-fluids are likewise increased. Many of the physical measures used therapeutically in the treatment of arthritis may achieve part of their benefit by the removal of fluid from tissues. Thus, local massage has been shown to increase urinary output [21] perhaps by virtue of the increased lymph flow and circulation of blood which is induced. Heat acts to increase extrarenal losses and probably also acts to influence the local distribution of fluids.

Rest in recumbency is generally regarded as an effective means of bringing about a removal of fluid from the tissues in frank edema. While arthritic patients do not present derangements of the circulatory system to

an extent which leads to frank edema they do occasionally present very persistent local edema. Pemberton and Peirce (unpublished) have observed in the skin capillaries a stasis or sluggish flow which might be considered as contributory to accumulation of fluid in the skin.

CHART IV

Approximate Water Exchange as Influenced by Qualitative Character of Diet



The recognized relationship of the plasma protein to the fluid accumulation in nephrosis suggested the desirability of determining the relation of plasma proteins to the type of swelling observed in arthritis. Experiments in the writers' laboratory, however, have failed to reveal any gross deviation from normal values for total protein among arthritic patients. The albumin-globulin ratios likewise appear to be within normal limits. There is, on the other hand, an increase in fibrinogen which is in general parallel to the increase in sedimentation rate. While the data do not permit a precise evaluation, it is possible that the increase of the protein fraction in plasma which alters the normal hydration of the red cells to the extent of increasing rouleau formation and the sedimentation rate, may also influence the distribution of fluids in tissues.

We believe that the swelling of tissues in arthritis is, in part at least, due to an excessive accumulation of fluids, and further, that dietetic and other measures which induce a reduction in swelling are associated with a net loss of fluid from the body.

Recognition of the probable participation of an abnormal distribution of fluid in the tissues, as part of the syndrome of arthritis, carries with it no implication that this explains the whole syndrome, nor should the implication follow that dehydration by any and all means constitutes a "cure" for arthritis. It is necessary only to point out that saline catharsis, intensive sweating and marked diuresis have been long and widely utilized, have been found to be only limited in value or even dangerous, and by general consent, do not as such constitute the "way out" for these patients. On the contrary emphasis should be placed upon measures or influences which operate in a more sustained way, without abrupt dislocation of function and without the imposition of further burdens.

Although clinical use of dietetic measures has had large substantiation in many hands and although laboratory studies of several kinds have adduced suggestive support, further precise data have been desirable. It is perhaps warranted, therefore, to point out that the considerations here advanced carry further justification for the use of these measures in the problem of arthritis. This is not to say, however, that the mechanism concerned in the influence of diet, above discussed, constitutes the only means by which dietary regulation may exert a beneficial influence in the treatment of arthritis. The experimental diets discussed are not to be confused with the optimal type of diet often necessary in treatment over long periods of time. Furthermore, the reader is hereby cautioned that the use of dietetic measures which we have described is not to be interpreted as a "blanket" form of therapy although probably having in principle some relation to most cases.

Summary

1. Attention is directed to the fact that convalescence from arthritis is frequently characterized by a reduction of soft tissue swelling, particularly evident though rarely conspicuous in the hands, and concurrent with a diminution of pain and increasing range of joint motion.

2. In a series of selected cases, approximate water balance estimations have indicated that a net loss of water from the body accompanies a subsidence of swelling of tissues, pain, and limitation of motion.

3. It is suggested that disturbances of water distribution in tissues constitute significant factors in the dynamic pathologic changes of the rheumatoid syndrome.

4. An attempt to evaluate the rôle of dietetic and other factors in this series of events has been made by studying the different phases contributing to the net result. The administration of several types of low calorie diets has been shown to be associated with a net loss of water and with clinical improvement.

5. Dehydrating diets, adequate in calories, high in protein, low in fluid and high in fat induced a net loss of water from arthritic patients with clinical evidence of improvement, and the suggestion is made that the relative in-

crease of fat and protein metabolized on low calorie diets exerts a significant influence in the striking clinical results frequently achieved.

6. Recumbent rest is considered as acting, in part, by favorably influencing a shift of fluid from the tissues to the blood and lymph channels.

7. Many seemingly unrelated factors which influence arthritis favorably when used within proper limits, such as dietetics, recumbent rest, heat and massage, may act in part by favoring fluid removal from tissues.

8. Attention is directed to the fact that a negative water balance contributes to recovery from both atrophic and hypertrophic arthritis. This suggests that both types of arthritis arise, in part, from similar or comparable premises; and further, that rigid restriction of many therapeutic measures, especially those here mentioned, to one type alone is unwarranted.

9. The relationships pointed out do not imply that dehydrating measures alone constitute a therapeutic escape from arthritis. Vigorous sweating, purgation or diuresis have long been known to be of only limited value, and even dangerous. So far as changes in the distribution of tissue fluids in arthritis may be desirable, they should be achieved by the more sustained and "physiological" influence and measures we have discussed.

10. Further justification is afforded for the controlled use of dietetic measures in the treatment of arthritis. The reader is again cautioned as to the dangers involved in uncritical employment of this agency.

The authors are indebted to Dr. Theodore F. Bach for assistance in clinical details and to Miss M. Robinson for supplying data on the weights and composition of the foods consumed by the patients.

BIBLIOGRAPHY

1. Adolph, E. F.: Metabolism and distribution of water in body and tissues, Physiol. Rev., 1933, xiii, 336–371.
2. Benedict, F. G., and Root, H. F.: Insensible perspiration; its relation to human physiology and pathology, Arch. Int. Med., 1926, xxxviii, 1–35.
3. Fletcher, A. A., and Graham, D.: Large bowel in chronic arthritis, Am. Jr. Med. Sci., 1930, clxxix, 91–93.
4. Kovacs, J.: Surface temperature and minute blood vessels of skin in arthritis, Jr. Am. Med. Assoc., 1933, c, 1018–1021.
5. Krogh, A.: The anatomy and physiology of capillaries, 1929, Yale University Press, New Haven.
6. McClure, W. B., and Aldrich, C. A.: Time required for disappearance of intradermally injected salt solution, Jr. Am. Med. Assoc., 1923, lxxxi, 293–294.
7. Peters, J. P.: Distribution and movement of water and solutes in human body, Yale Jr. Biol. and Med., 1933, v, 431–467.
8. Pemberton, R.: Arthritis and rheumatoid conditions; their nature and treatment, 1929, Lea and Febiger, Philadelphia.
9. Pemberton, R.: Work of American Committee for Control of Rheumatism; present status of arthritis, Med. Jr. and Rec., 1933, cxxxviii, 359–363.
10. Pemberton, R.: Studies on arthritis in army based on four hundred cases, Arch. Int. Med., 1920, xxv, 351.
11. Pemberton, R., Hendrix, B. M., and Crouter, C. Y.: Studies in arthritis; blood gases and blood flow, Jr. Metab. Res., 1922, ii, 301–328.
12. Pemberton, R., and Osgood, R. B.: The medical and orthopaedic management of chronic arthritis, 1934, The Macmillan Co., New York.

13. PEMBERTON, R., and PEIRCE, E. G.: Relation of intestinal tract and diet to treatment of arthritis, ANN. INT. MED., 1932, v, 1221–1237.
14. PEMBERTON, R., PEIRCE, E. G., and BACH, T. F.: Relation of vitamins to dietetic treatment of arthritis, Med. Jr. and Rec., 1933, cxxxviii, 445–449.
15. PEIRCE, E. G.: The red cell count in arthritis (first paper), Arch. Int. Med., 1927, xxxix, 421–428.
16. ROWNTREE, L. G., and ADSON, A. W.: Bilateral lumbar sympathetic ganglionectomy and ramisectomy for polyarthritis of lower extremities, Jr. Am. Med. Assoc., 1927, xxxviii, 694–696. Polyarthritis; further studies on effects of sympathetic ganglionectomy and ramisectomy, Jr. Am. Med. Assoc., 1929, xciii, 179–182.
17. SPARKS, M. I., and HADEN, R. L.: Blood volume in chronic arthritis, Am. Jr. Med. Sci., 1932, clxxxiv, 753–757.
18. WILEY, F. H., and NEWBURGH, L. H.: Improved method for determination of water balance, Jr. Clin. Invest., 1931, x, 723–731.
19. WRIGHT, L. M., and PEMBERTON, R.: Peripheral surface temperature in arthritis, Arch. Int. Med., 1930, xlv, 147–158.
20. NISSEN, H. A., and SPENSER, K. A.: Sugar tolerance in the arthritic, New Eng. Jr. Med., 1934, ccx, 13–19.
21. CAJORI, F. A., CROUTER, C. Y., and PEMBERTON, R.: Physiologic effect of massage; second contribution, Arch. Int. Med., 1927, xxxix, 281–285.

SOME OBSERVATIONS ON MERCURIAL DIURETICS*

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The use of mercury as a diuretic was advocated first by Jendrássik[1] in 1886. He administered frequent small doses of calomel by mouth and by this means obtained in many cases a marked increase in urine volume. Gradually this form of treatment fell into more or less disuse as observers reported deleterious effects as a result of the mercury absorbed. In recent years, following the introduction of the complex organic compound of mercury, novasurol, first described by Saxl and Heilig[2] in 1920, mercury has again assumed a prominent place in the treatment of edematous conditions. The favorable results which the above investigators reported have been abundantly confirmed. As with all complex drugs other similar combinations were sought which would produce, if possible, greater results with less toxicity. Although toxic symptoms from novasurol were comparatively rare it came to be replaced by salyrgan which also induced marked diuresis but with fewer toxic manifestations. The literature relating to both of these substances has been fully reviewed recently by Binger and Keith[3] and by Schmitz.[4] In order to intensify the action of the mercurial diuretics efforts have been made to combine their use with other substances which were also known to produce an increase in urine volume. Keith, Barrier and Whelan[5] noted very beneficial results as a result of a combination with ammonium chloride while more recently Herrmann and his coworkers[6,7] have shown that theophylline and salyrgan given together induce a greater effect than the use of either alone. The former has been recognized as a potent diuretic since its action was described by Von Schroeder.[8] The latest mercurial diuretic introduced is one in which a complex mercurial salt is combined with theophylline.† The mercury content of this drug is essentially similar to that in novasurol and salyrgan. Excellent clinical results and a low incidence of toxicity have been reported by Hahn,[9] Popper,[10,11] Saxl,[12] Spengler,[13] and Pratsikas.[14] The present investigation was undertaken to study the effect of this preparation and to observe whether it offered any advantages over those in common use.

Method of Investigation

The patients on whom the observations were carried out remained at rest in bed. High carbohydrate diets were used and one gram of sodium chloride was given per diem. The daily fluid intake was restricted to 1200

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From the Department of Cardiology, Kings County Hospital, and the Department of Physiology and Pharmacology of the Long Island College of Medicine.
† Originally introduced as Novurit, this drug is sold in America under the name of Mercupurin.

c.c. In the cardiac cases the patients were fully digitalized before the mercurial diuretics were given and were continued on a maintenance dose throughout the period of observation. In most instances xanthine diuretics had been unsuccessfully used before commencing the mercurial group. In fact before the period of study, many had had fluid removed mechanically from the abdominal or thoracic cavities. Preparatory to the administration of the mercurial diuretics the urine volume in 24 hours was carefully measured until it remained practically steady for a period of at least three days.

The mercurial diuretics were used in doses of one to two c.c. intravenously in every instance. As a rule a preliminary injection of one c.c. was given to determine the possibility of an idiosyncrasy. Thereafter, as a rule the dose was two c.c. Usually the injections were repeated at intervals of four days although in one case which showed a particularly good response only two days were allowed to elapse. The intake and output of fluids were carefully measured throughout the period of study. When the diuresis was prolonged beyond 24 hours the total for the following day minus the normal average output without the drug was included in the total diuretic response. Changes in weight were not followed as many of the patients were so sick that it was inadvisable to get them out of bed to weigh them. At frequent intervals, particularly on the day following injection, the urine was carefully studied for albumin and blood cells in order to be certain that renal injury was not produced. In many instances blood urea nitrogen estimations were also performed throughout the study. More injections of mercupurin were given than of salyrgan. The latter, however, was not administered after all the observations on the former had been made but spaced irregularly during the period of investigation.

Results

Fifteen patients, all in advanced stages after long periods of invalidism, were studied. Ten suffered from heart disease and five from cirrhosis of the liver. They received a total of 118 injections of mercupurin and 20 of salyrgan. It was considered inadvisable when trying a new mercury preparation to use patients in whom any marked degree of kidney damage was present in view of the great liability of the kidney to injury by mercury.

In every instance the administration of the diuretic was followed by an increase in the output of urine, often to a very marked degree. The diuresis commenced as a rule within three hours and attained a maximum in about eight to 12 hours. Generally the effect passed off in 24 hours but sometimes it persisted during the following day. In no instance was it prolonged beyond this period. As had been noted by other observers, frequent repetition of the drug often tended to lessen the urine volume after later injections, even in those cases in which there was considerable edema fluid still present.

The results in individual cases both with mercupurin and salyrgan are presented in table 1. In each patient the maximum and minimum outputs

are given for different doses of a particular drug and also an average for all injections of the same dose. Figure 1 illustrates in each case the average

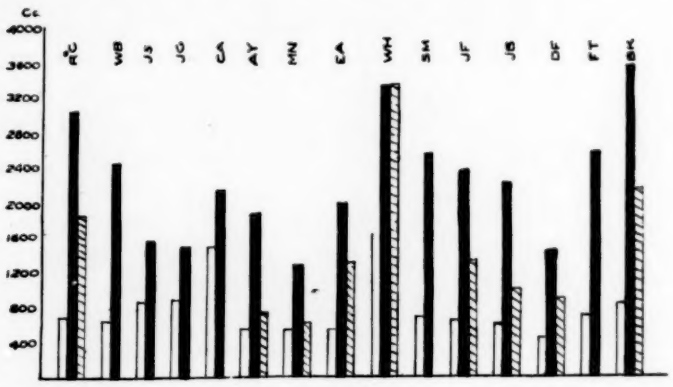

FIG. 1. The average urine volume in the different cases following the administration of mercurial diuretics. (Plain blocks—normal; solid blocks—mercupurin; cross-hatching—salyrgan.)

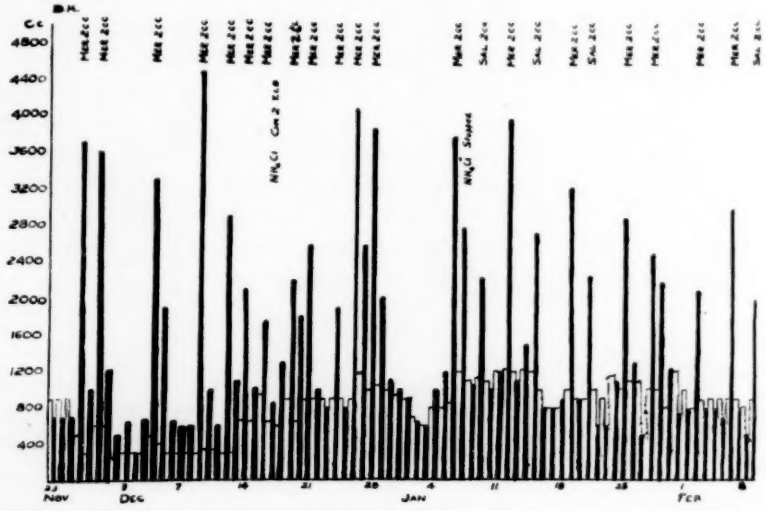

FIG. 2. The response to the administration of mercurial diuretics throughout the period of study in case B.K. (Plain blocks—intake; solid blocks—output; Mer—mercupurin; Sal—salyrgan.)

urine volume without mercurial diuretics and that after mercupurin and salyrgan. Figure 2 shows a case which responded particularly well to this type of diuretic. In every instance, except one, in which mercupurin and salyrgan were compared, the response to the former was greater than to the latter. In some cases, during part of the period of observation ammonium chloride, gm. 8 per diem, was given and generally there was some increase in the response both with mercupurin and salyrgan.

TABLE I

Case	Diagnosis	Average daily intake c.c.	Average daily output before drug c.c.	Urine volume in c.c. during period of diuresis									
				Mercupurin					Salyrgan				
				Dose c.c.	No. of inject.	Max.	Min.	Av.	Dose c.c.	No. of inject.	Max.	Min.	Av.
R.C.	Hypertensive heart disease	800	700	1 2	1 2	4150	2100	1100 3125	2	1			1850
A.Y.	Mitral stenosis Aortic insuff.—rheumatic	732	588	1 2	1 10	2700	1200	360 1861	1 2	1 1			840 660
M.N.	Aortic insuff.—luetic	738	566	2	14	3212	500	1298	2	2	800	500	650
E.A.	Mitral stenosis—rheumatic	771	559	1 2	2 4	3141 2261	2221 1361	2681 1655	1	1			1320
W.H.	Arterio-sclerotic heart disease	809	1638	1 2	2 2	4200 3762	3362 2000	3781 2881	2	2	3600	3100	3350
S.M.	Arterio-sclerotic heart disease	1028	696	1 2	1 7	3100	1000	6500 2000					
W.B.	Mitral stenosis—rheumatic	900	750	2	6	3650	1300	2450					
J.S.	Arterio-sclerotic heart disease	700	830	1	2	2200	950	1578					
J.G.	Arterio-sclerotic heart disease	1150	900	1 2	1 1			1700 1300					
C.A.	Mitral stenosis—rheumatic	981	1509	2	4	2550	1650	2137					
B.K.	Cirrhosis of liver	820	820	2	20	5880	1750	3535	2	4	2750	2000	2332
J.F.	Cirrhosis of liver	979	682	1 2	1 4	3718	1050	3218 2159	1 2	1 3	1500	900	1950 1167
J.B.	Cirrhosis of liver	850	600	1 2	1 8	3400	1000	1500 2170	2	2	1400	600	1000
D.F.	Cirrhosis of liver	710	450	1 2	1 2	1800	850	550 1325	2	1			900
F.T.	Cirrhosis of liver	1028	696	1 2	1 7	3100	1000	6500 2000					

Evidences of Clinical Improvement

In most instances there was striking improvement in the condition of the patient. R.C., suffering from ascites and edema of the legs, was rendered edema free. A.Y., who had extreme edema which had persisted for many months and had failed to respond to all forms of treatment including salyrgan, showed a marked reduction in the edema after mercupurin injections. Although abdominal paracentesis had previously to be performed at frequent intervals, this had only to be done once after this type of treatment was instituted. M.N. at first responded in a satisfactory manner but later failed to show any benefit. E.A. was rendered edema free and ascites disappeared. W.H., prior to the use of mercurial diuretics, required the removal of fluid from either the pleural cavity or abdomen at weekly intervals but the injections produced such marked relief that after this treatment the chest had to be tapped on only one occasion and ascites did not reaccumulate. S.M., who at the beginning of the study had edema of the legs, ascites and right hydrothorax, was rendered edema free. W.B. had massive edema of the extremities and marked ascites both of which were completely removed. J.S. suffered from marked ascites which was relieved on discharge. J.G. showed moderate edema which disappeared. C.A. had ascites and edema of the legs, both of which were absent after treatment. B.K. required abdominal paracentesis at weekly intervals before mercurials were used but thereafter only had one tapping in two and a half months. J.F. responded well to the drugs but died despite the relief of the ascites. J.B. had fluid removed from the abdomen at six to 12 day intervals over a period of three months but after the injections were instituted the ascites disappeared. D.F. did not give a satisfactory response and slowly accumulated fluid despite the use of any form of diuretic. F.T. required frequent abdominal paracentesis but after the use of mercurial diuretics this had not to be repeated.

Evidences of Toxicity

In no case was there any reaction following the injection of either drug. The urine studies showed no evidence of renal damage while the blood urea, even in those cases in which it was slightly elevated, remained essentially the same after many injections had been given. A possible explanation of the lack of evidence of toxicity may be that no cases were used which showed marked renal involvement. Binger and Keith [8] found that these were most likely to show toxic phenomena although such phenomena sometimes presented in patients with hepatic damage. The lowest incidence occurred in heart cases which constituted the majority of cases in our series.

Discussion

The problem of diuresis is one which has been subjected to much investigation but the importance of the removal of edema fluid is such that

every effort should be made to improve the methods of dealing with a sign of such grave import. That the mercurial diuretics have proved a marked advance in this respect is unquestioned. Our results demonstrate that most satisfactory results were obtained by their use in almost every instance while evidences of toxicity were absent. All cases had received other forms of diuretics without any benefit and apparently offered a very bad prognosis. In several instances the administration of the mercurial preparations merely prolonged life for a period, but in many others the patients were returned to a life of some usefulness. Even in the former the symptomatic relief was very marked and the comfort of the patient materially increased.

A great deal of discussion has arisen as to the mode of action of the various forms of diuretics. As regards the mercurial diuretics it is agreed that changes in the circulation play no part. However, there is a divergence in the point of view as to whether the action is on the extra-renal tissues or on the kidney itself. In their original communication Saxl and Heilig [2] favored the former. Crawford and McIntosh,[15] in their investigation, found that although there might be some evidence for this during a very short period after the drug was administered, it was unimportant compared to the renal effect. Many investigators have supported one or other viewpoint. The literature is fully reviewed by Schmitz.[4] Both the latter and Herrmann and his co-workers [6, 7] have utilized the Rehberg method of calculating the amount of glomerular filtration and the amount of tubular reabsorption in the study of this problem. Each concluded that the mercurial diuretics act mainly by decreasing tubular reabsorption. In a later paper Schmitz [16] stated that he found no evidence of extra-renal action. Lassen,[17, 18] however, using a similar method obtained a decrease in glomerular filtration in normal individuals after salyrgan but an increase in cases of cardiac edema in which the initial value was low. Further evidence of a direct action on the kidney is furnished by the experiments of Bartram [19] in which he injected salyrgan into one renal artery. With a small dose there was a diuresis from that kidney and none from the other.

The mode of action of the xanthine diuretics is similarly the subject of much discussion. Von Schroeder [8] believed that it was independent of the circulation while another school considered that circulatory changes were the main factor. Others stated that the seat of action was the extra-renal tissues while another group believed that a renal effect was responsible. Even the latter disagreed as to whether the action was on the glomeruli or the tubules. This subject is fully discussed by Schmitz.[4] He, as well as Herrmann and his associates,[6, 7] in the investigations referred to above, also studied the xanthine group. Both state that there was a marked increase in glomerular filtration while the changes in tubular reabsorption were slight and inconstant. Davenport, Fulton, Van Auken, and Parsons [20] as a result of their studies on dogs conclude that the Rehberg method does not give an accurate index of glomerular filtration. Blumgart and his associates,[21]

using a modified Rehberg method, were unable to demonstrate any increase in the amount of glomerular filtrate with either euphyllin or salyrgan.

A review of the literature at the moment seems to indicate that both the xanthine and mercurial diuretics have their main action on the kidney, the former increasing glomerular filtration and the latter retarding tubular reabsorption. However, further investigation must take place before final conclusions are made. Assuming that this view is correct, there appears to be a sound theoretical basis for the use of a combination of these two types of diuretic.

Conclusions

1. A combination of an organic mercurial compound with theophylline has been investigated on a series of cases of advanced heart failure and cirrhosis of the liver. In every instance a satisfactory increase in urine volume was produced without toxic effects.

2. This preparation was compared with the results of injecting an organic mercurial preparation alone, and in every instance except one the average diuresis was greater in the former.

3. The theoretical advantages of such a combination are discussed.

REFERENCES

1. Jendrássik, E.: Das Calomel als Diureticum, Deutsch. Arch. f. klin. Med., 1886, xxxvii, 499–524.
2. Saxl, P., and Heilig, R.: Über die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, Wien. klin. Wchnschr., 1920, xxxiii, 943.
3. Binger, M. W., and Keith, N. M.: Effect of diuretics in different types of edema, Jr. Am. Med. Assoc., 1933, ci, 2009–2016.
4. Schmitz, H. L.: Studies on action of diuretics; effect of euphyllin and salyrgan upon glomerular filtration and tubular reabsorption, Jr. Clin. Invest., 1932, xi, 1075–1097.
5. Keith, N. M., Barrier, C. W., and Whelan, M.: Diuretic action of ammonium chloride and novasurol in cases of nephritis with edema, Jr. Am. Med. Assoc., 1925, lxxxv, 799–806.
6. Herrmann, G., Stone, C. T., Schwab, E. H., and Bondurant, W. W.: Diuresis in patients with congestive heart failure, Jr. Am. Med. Assoc., 1932, xcix, 1647–1652.
7. Herrmann, G., Schwab, E. H., Stone, C. T., and Marr, W. L.: On advantage of alternating vegetable and metallic diuretics in treatment of edema of congestive heart failure, Jr. Lab. and Clin. Med., 1933, xviii, 902–915.
8. Von Schroeder, W.: Über die Wirkung des Caffeins als Diureticum, Arch. f. exper. Path. u. Pharmakol., 1886–1887, xxii, 39–61.
9. Hahn, A.: Novurit, ein neues Diuretikum, Wien. klin. Wchnschr., 1929, xlii, 1477–1478.
10. Popper, L.: Ein neues Quecksilber-Diuretikum "Novurit", Med. Klin., 1929, xxv, 912–913.
11. Popper, L.: Weitere Erfahrungen mit dem Quecksilber-Diuretikum "Novurit," Med. Klin., 1930, xxvi, 1229–1230.
12. Saxl, P.: Fortschritte der Diuresetherapie, Wien. med. Wchnschr., 1930, lxxx, 293–295.
13. Spengler, G.: Zur Therapie der Leberzirrhose, Wien. klin. Wchnschr., 1931, xliv, 257–259.
14. Pratsikas, A.: Das Quecksilber-Diuretikum "Novurit" in der Klinik, Wien. med. Wchnschr., 1933, lxxxiii, 28–30.

15. Crawford, J. H., and McIntosh, J. F.: Use of novasurol in edema due to heart failure, Jr. Clin. Invest., 1925, i, 333–358.
16. Schmitz, H. L.: Studies on action of diuretics; effect of salyrgan upon water content of plasma as measured by refractive index, Jr. Clin. Invest., 1933, xii, 741–750.
17. Lassen, H. C. A.: Studies on kidney function after Rehberg method; variations of filtration in normal adults, Acta med. Scandinav., 1932, lxxix, 275–297.
18. Lassen, H. C. A.: Some investigations on kidney function in heart lesions, Acta med. Scandinav., 1932, Suppl. 50, 216–413.
19. Bartram, E. A.: Experimental observations on effect of various diuretics when injected directly into one renal artery of dog, Jr. Clin. Invest., 1932, xi, 1197–1219.
20. Davenport, L. F., Fulton, M. N., Van Auken, H. A., and Parsons, R. J.: Creatinine clearance as measure of glomerular filtration in dogs with particular reference to effect of diuretic drugs, Am. Jr. Physiol., 1934, cviii, 99–106.
21. Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M. G., and Volk, M. C.: Action of diuretics. I. Action of diuretics in normal persons, Arch. Int. Med., 1934, liv, 40–81.

CUTANEOUS TUBERCULOSIS AND GENERAL MEDICAL DIAGNOSIS *

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The diseases of the skin which are recognized as bearing some relationship to tuberculosis have in recent years been so increased in number that the subject is now a complex one, and of great importance in its respect to general medical diagnosis.

The cutaneous disorders associated with tuberculosis are readily divisible into two groups. In the first are found those dermatoses which are universally accepted as due to the tubercle bacillus, and which show a pathological picture not differing materially from that seen in other organs of the body affected by tuberculosis. Lupus vulgaris, scrofuloderma, tuberculosis cutis orificialis and tuberculosis verrucosa cutis are included here. These disorders are as a rule generally recognized and their significance appreciated.

The second group is the one with which we are particularly concerned, as it consists of a large number of dermatoses whose relationship to tuberculosis is in some types definitely proved, and in others only doubtful.

Although for many years a number of dermatoses had been observed in which an association with tuberculosis had been suspected, it was not until 1896 that Darier placed in a single group these eruptions whose manifestations did not correspond at all to the picture of cutaneous tuberculosis seen in the members of the first group. He called attention to the fact that there existed a number of cutaneous disorders which occurred in individuals suffering with tuberculosis and which had a number of features in common, among these being a benign course, tendency to spontaneous cure, wide and symmetrical disposition, tendency to recurrence in successive crops without fever and a varied histological picture often suggestive of tuberculosis.

From time to time additions have been made to the list of tuberculides, until at present we have a group of some 25 disorders in which it has been suggested that a systemic tuberculosis is responsible for the eruption. In the case of four of these conditions, i.e., erythema induratum, lichen scrofulosorum, acnitis, and folliclis, it is generally conceded that tuberculosis is responsible for the eruption, while with the other members of the group the evidence of such a relationship varies from almost conclusive to very slight.

As to the manner in which the systemic infection produces these disorders, there are various theories. They were at first thought to be due to the action of toxins elaborated by the tubercle bacillus in its primary focus and carried to the skin by the blood stream. Others felt that they were due to dead bacilli circulating in the blood, to the production of microbic emboli by organisms of low or attenuated virulence, or to a special filterable form

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

of the bacillus. Avian and bovine types of organisms were also suggested as the responsible agents. In 1914 Rist and Rolland [1] contributed the theory which has gained widest acceptance. After extensive research, they concluded that the tuberculides occur in individuals who, as a result of a latent or manifest form of tuberculosis, have developed a state of allergy, the tuberculides thus representing the reaction of the sensitized skin to the tubercle bacilli carried to it by the blood stream from a visceral or other focus of infection. The tuberculide lesions therefore represent spontaneous examples of Koch's phenomenon resulting from endogenous inoculation of the skin, and the ensuing destruction of the bacteria accounts for the spontaneous healing as well as for the infrequency with which tubercle bacilli are found in the cutaneous lesions. This theory is supported by the fact that the bacilli can be demonstrated much more frequently if very early lesions, i.e., those in which the allergic reaction has not developed to the point of destruction of the organisms, are selected for examination. Wise has summarized this by stating that the variations in form and type of eruptions provoked by the tubercle bacillus seem to depend upon three factors: (1) the individual disposition of the patient; (2) the number of bacilli circulating in the blood stream; and (3) the degree of immunity reaction residing in the affected organism.

More recent than the above theory, but not generally accepted, is the idea that the tubercle bacillus presents in its life cycle a virus or a granular form, and that these forms of the organism are responsible for the development of tuberculides.

A number of writers have called attention to the diagnostic importance of those members of the tuberculide group which are generally accepted as being due to tuberculosis, and to the fact that the physician all too frequently fails to recognize their significance. The presence of an eruption of lichen scrofulosorum, papulo-necrotic tuberculides (acnitis and folliclis) or erythema induratum, if properly diagnosed, should instigate a search which will frequently disclose an unsuspected focus of tuberculosis, most often in the lymph glands, but at times in bones, joints, the intestines or other parts. Active tuberculosis of the lungs is infrequent with these disorders. At times, as Goeckerman [2] has pointed out, they are of value in disclosing the source of disturbance in cases where the symptoms are obscure, where only the presence of tuberculides may suggest the source of frequent headache, malaise, vague pains, asthenia, lack of endurance and obscure fever. Their presence is taken to indicate an active though chronic tuberculous infection which gives rise to periodic attacks of bacillemia, resulting in the formation of embolic obstruction of the vessels of the skin and subcutaneous tissue.

As evidence of the frequency with which the value of these eruptions is overlooked may be cited the observation of Stokes,[3] who found that in only five of his cases of papulo-necrotic tuberculide had a correct diagnosis been made, and 57 per cent of the cases showed incontrovertible objective evidence of tuberculosis and 13 per cent had disputable signs; and that of Hayes,[4]

who reported three cases of the same type, two of them in patients with active pulmonary tuberculosis, and pointed out that each of the patients had been seen by a number of physicians whose work was devoted largely to tuberculosis, and the lesions diagnosed as anything from simple dermatitis to syphilis and leprosy.

It is impossible to consider all the other and less well established members of the group of tuberculides, but in the case of three of the disputed ones, erythema nodosum, erythema multiforme and the sarcoids, developments of recent years have been of interest.

With regard to erythema nodosum and a possible tuberculous etiology, interest has been widespread in the last few years only, although Willan in 1798 was probably the first to remark upon the connection of these two diseases, when he noticed that tuberculosis occasionally followed an attack of this eruption. Uffelman [5] in 1876 and Poncet [6] in 1902 were other early observers of this association. Pons [7] in 1905 showed giant cells in sections of a nodule of erythema nodosum and also called attention to the development of typical nodules in an individual after a diagnostic dose of tuberculin. Brian produced tuberculosis in three guinea pigs by injecting blood from a patient who had erythema nodosum, but who had no clinically recognizable tuberculosis. Landouzy [8] described erythema nodosum as a complication in a case of tuberculosis septicemia, and another case of the same disorder in which he was able to find a single acid fast bacillus in the lumen of a vessel in one of the lesions, and inoculation of a guinea pig gave positive results.

In 1912 Pollak [9] reported a study of 42 cases seen during a two year period. Although the patients ranged in age from one to 13 years, so that tuberculosis would not be expected frequently, all gave positive reactions to tuberculin. The tests were still positive months later, and in three of the cases definite tuberculosis developed within three to 10 months, while others showed evidence of phlyctenules and tuberculosis of the bones.

Ernberg [10] saw 35 children with erythema nodosum between 1908 and 1914, and was able to examine personally 31 of these patients during 1916 and 1917. Not one of the patients had developed any signs of rheumatism, but 13 showed symptoms of tuberculosis and one had died of miliary tuberculosis.

Vetlesen,[11] who regards erythema nodosum as a danger signal, found that 5.1 per cent of his patients with pleurisy had previously had erythema nodosum, as had 0.9 per cent of the patients with other manifestations of tuberculosis. Symes [12] found that 10 per cent of his cases of erythema nodosum showed tuberculous disease within six months, and in a later report recorded three more cases of erythema nodosum, in two of which tuberculosis developed later.

In spite of strong evidence of an association between erythema nodosum and tuberculosis shown by these and numerous other observations, the findings could not be considered conclusive. Symes stated that "There is an undeniable association between erythema nodosum and tuberculosis. The

evidence in support of this fact is strong on the clinical side. Tuberculin tests and skiagraphy in the hands of experts afford confirmatory evidence of high value. The pathological and bacteriological evidence is weak." Wallgren [13] has added valuable support in the latter field, in reporting on the results of examination of the stomach washings by the method of Meunier in 40 children suffering with erythema nodosum. Thirty-seven of these reacted positively to tuberculin, and in 17 of these tubercle bacilli were found after guinea pig inoculation. Collis confirmed this in three out of five tuberculin positive cases.

Dickey [14] in 1932 found 100 per cent of 16 patients under 15 years of age with erythema nodosum to have positive tuberculin reactions. The majority of his patients were girls, and all the patients gave positive reactions to tuberculin and most of them to minimal doses. In four of them the rash followed the use of tuberculin. In most of the cases a perifocal reaction was demonstrated by roentgen-ray examination.

Saenz et al.[15] recently reported the case of a woman aged 30 years who developed erythema nodosum. The tuberculin reaction was positive and a tracheo-bronchial adenopathy was shown by roentgen-ray examination. He injected the sediment of centrifuged blood taken from the patient into guinea pigs. Both of these died of intercurrent infections, but showed gland involvement with numerous acid fast bacilli present. Material from these glands produced generalized tuberculosis in guinea pigs. Material from one of the skin lesions was injected into four guinea pigs. Only two survived. Of these, one showed no signs of tuberculosis, but the other developed enlarged glands in which only a few acid fast bacilli were found. Material from these glands injected in other guinea pigs produced large caseating glands with numerous bacilli present. The authors interpret these findings as indicating that even with a profuse bacillemia the organisms in the skin lesion are few in number, thus explaining the difficulty of demonstrating them in sections.

Wallgren [16] has reported an observation of 36 girls of about 10 years of age in a single classroom, 18 of whom had erythema nodosum. Later all of these so affected gave positive Pirquet reactions and 13 had changes about the hilum demonstrable by roentgen-ray, and four others showed definite changes. He found an open case of tuberculosis in one of the girls in the class, and regarded this as the source of infection.

Massini and Bale [17] in 29 cases of erythema nodosum found tuberculous involvement in 14. Ernberg,[18] reporting again in 1932, states that all of his investigations and those of other writers led him to believe that erythema nodosum can be explained as an autogenous tuberculin reaction. He feels with Wallgren that this cutaneous picture usually develops at an early stage of tuberculosis, appearing at a time which can be regarded as the end of the incubation period, i.e., the time at which the allergy to the disease becomes established as shown by the development of a positive reaction to ordinary doses of tuberculin. He regards erythema nodosum as a sign of

active tuberculosis, whether it appears thus at the transition between the preallergic and allergic states in a newly infected person, or in connection with an acute infectious disease or other agencies activating a previously existing tuberculosis.

In the experience of most observers erythema nodosum is associated with a focus of tuberculosis in the region of the hilar glands, but the focus may be found in other areas.

While not all writers are in accord as to the exact character of the relationship between tuberculosis and erythema nodosum, practically all who have studied the subject agree that such an association exists, particularly in erythema nodosum occurring in children. Symes, Wallgren and Ernberg, among others, urge that patients who have suffered erythema nodosum be allowed a long period of convalescence with open air treatment and extra feeding. It is urged that all children who have had erythema nodosum undergo a roentgen-ray examination for changes in the region of the hilum. The early detection of tuberculous involvement is not only of value to the child, but also by preventing his return to school will save other children from exposure to tuberculous infection.

It is not to be inferred that even in children erythema nodosum should be regarded as due to tuberculosis in every instance, as the same clinical picture may be caused by other infections, principally streptococcic, and by the ingestion of drugs.

There are, however, in many cases of tuberculous origin, certain clinical differences which may aid in the determination of the etiology. In the tuberculous variety the lesions are apt to occur in unusual locations, with a greater tendency to localize on the posterior aspects of the legs. The nodules are smaller, tend to be less numerous, and the inflammatory reaction is less acute. The process as a whole is less active, the lesions being less tender and more persistent, at times lasting for some months. In rare instances these persistent lesions may change in type and present the classic picture of erythema induratum, even going on to ulceration.

With regard to tuberculosis as a cause of erythema multiforme, the evidence is much less abundant and not as convincing. The possibility of a causative relationship here was probably considered largely because of the recognized association of erythema nodosum and erythema multiforme. Ramel [19] of Lausanne has been the chief proponent of this idea. He is convinced of the tuberculous nature of lupus erythematosus, and because of a clinical relationship seen at times between this disorder and erythema multiforme was led to seek a common etiology, particularly after he had seen papulo-necrotic tuberculides appearing on the fading lesions of an eruption of erythema multiforme. In an exhaustive report, Ramel stated that in eight cases of erythema multiforme he was able to demonstrate Koch's bacillus in the blood of all the patients and in the lesions of two of them, while in a later report the number of cases was increased to twenty-one. None of the patients presented traces of active tuberculous infection and

none gave a history of previous infection. He states that the type of tuberculosis is peculiar in that it can only be demonstrated by inoculation of guinea pigs. In the first inoculation no typical changes are produced in the animal. By successive inoculation of material taken from this and succeeding animals, a typical inoculation tuberculosis is secured, with a gradual appearance of acid fast bacilli in conjunction with the increase in the virulence of the infection. He believes that his method demonstrates that in the guinea pig there can exist a benign tuberculosis, characterized by non-follicular lesions, and that a tuberculous virus which can determine this type of infection in the guinea pig is present in the blood of patients suffering from erythema multiforme who do not present any clinical manifestation of tuberculosis as usually interpreted. The classic erythema multiforme of Hebra is interpreted by Ramel therefore as a non-follicular type of tuberculous manifestation, of hematogenous origin.

Percival and Gibson [20] and Hallam and Edington [21] have each investigated 10 cases of erythema multiforme, duplicating the method of Ramel, and in none of the 20 has it been possible to duplicate his findings.

It can only be said on the basis of the evidence thus far brought forth that the idea that erythema multiforme is of tuberculous etiology has not been established, but infection with tubercle bacillus must nevertheless be regarded as a possible cause in a certain proportion of the cases of this disorder which is generally looked upon as a complex of varied etiology. Stokes [3] includes this disorder with erythema nodosum and purpura as diseases which are of great diagnostic and prognostic significance in regard to tuberculosis.

With regard to the sarcoids, Boeck and Darier, who originally described the two types known respectively as benign miliary lupoid or multiple benign sarcoid and the subcutaneous sarcoid of Darier-Roussy, believed the disorder to be of tuberculous origin, but this view is not universally accepted at present, although the majority of observers support the idea, and many are willing to accept these lesions as proved tuberculides. The opposition to this view is in part due to the fact that syphilis, leprosy and other disorders may produce lesions which may resemble the sarcoid and which may be wrongly included under this heading. Opponents of the tuberculous theory point out the infrequency with which tubercle bacilli are found in the lesions and the usual negative results of inoculation of tissue into guinea pigs in support of their opinion, but Kyrle, who believes that the lesions of sarcoid represent a foreign body reaction to the tubercle bacillus and its disintegration products, has shown that the organisms are present only in the very early lesions, which have not as yet developed the characteristic histopathologic picture as the allergic reaction rapidly destroys them, thus accounting for the failure to demonstrate the organism in the fully developed lesion and for the failure of inoculation experiments.

The tuberculin test is almost always negative in patients with sarcoid, but Jadassohn and others have explained that in this group, in contradistinc-

tion to the hyperergic state which exists in the case of other types of tuberculides, the allergy has progressed almost to the state of desensitization, resulting in a condition of hypoergy or even anergy.

One of the most interesting aspects of the sarcoids is the frequency with which the skin lesions are associated with changes in other parts of the body, principally nodular infiltrations of the lungs, fibrocystic changes in the bones (especially in connection with the lupus pernio type of lesion), splenomegaly and adenopathy. Since these systemic changes in conjunction with sarcoids were first described, more careful observation has shown one or more of them to be demonstrable in a considerable proportion of cases.

Summary and Conclusions

The proved tuberculides, lichen scrofulosorum, papulo-necrotic tuberculides and erythema induratum, disorders of relatively frequent occurrence, furnish diagnostic and prognostic indices in tuberculosis which are often not diagnosed or appreciated. Their presence usually indicates an active though usually chronic form of tuberculosis most often involving the glands, bones and joints. Their presence indicates a high degree of resistance to the tuberculous infection, and therefore the prognosis as to the course of the latter is usually good.

Erythema nodosum, while undoubtedly a disease of complex etiology, is in some instances, and particularly in children, due to infection with tuberculosis. It tends to occur early in the course of the latter disease, and should indicate the advisability of insisting upon a prolonged convalescence and careful observation for a period of at least six months.

Erythema multiforme has not been established as a tuberculide, but there is evidence sufficiently suggestive to indicate that tuberculous infection may be responsible for a small proportion of cases.

The evidence would indicate that the sarcoids, together with the changes found frequently in other structures, can best be accounted for on a tuberculous basis.

BIBLIOGRAPHY

1. Rist, E., and Rolland, J.: Étude sur la réinfection tuberculeuse; la réinfection cutanée et le phénomène de Koch, Ann. de méd., 1914, ii, 13–54.
2. Goeckerman, W. H.: Tuberculids, Minn. Med., 1930, xiii, 462–464.
3. Stokes, J. H.: Cutaneous aspects of tuberculosis, Am. Jr. Med. Sci., 1919, clvii, 157, 313, 522.
4. Hayes, E. W.: Tuberculids, Am. Rev. Tuberc., 1923, viii, 288–296.
5. Uffelman, J.: Deutsch. Arch. f. klin. Med., 1872, x, 454; 1876, xviii, 313.
6. Poncet, A., quoted by Bronson, E.: Erythema nodosum, Brit. Jr. Child. Dis., 1918, xv, 91.
7. Pons, J.: Érythème noueux d'origine tuberculeuse. Tuberculose inflammatoire. Rheumatisme articulaire tuberculeux, 1905, Lyon.
8. Landouzy, L.: Assoc. Franc. pour l'avancement des Sci., 1907, xxxvi, 337.
9. Pollak, R.: Erythema nodosum und Tuberkulose, Wien. klin. Wchnschr., 1912, xxv, 1223–1225.

10. Ernberg, H.: Quoted by Vetlesen.[11]
11. Vetlesen, H. J.: Erythema nodosum and tuberculosis, Tubercle, 1922, iii, 433–440.
12. Symes, J. O.: Erythema nodosum and tuberculosis, Clin. Jr., 1923, lii, 189–191.
13. Wallgren, A.: New argument in favor of tuberculous nature of erythema nodosum, Acta pediat., 1930, xi, 590–591; Am. Jr. Dis. Child., 1931, xli, 816.
14. Dickey, L. B.: Erythema nodosum and tuberculosis in children, Am. Rev. Tuberc., 1932, xxvi, 614–624.
15. Saenz, A., Chevallier, P., Lévy-Bruhl, M., and Costil, L.: Sur la présence du bacille de Koch virulent dans les lésions cutanées et dans le sang d'une malade en plein accès d'érythème noueux, Compt. rend. Soc. de biol., 1933, cxii, 951–953.
16. Wallgren, A.: Erythema nodosum, Acta pediat., 1926, v, 225–253.
17. Massini and Bale, quoted by Schacter, M.: L'érythème noueux et son importance pour le médicin d'enfants, Jr. de méd. de Lyon, 1932, xiii, 677–680.
18. Ernberg, H.: Erythema nodosum and tuberculosis, Am. Jr. Dis. Child., 1933, xlvi, 1297–1307.
19. Ramel, E.: Some observations on causation of erythema exudativum multiforme (Hebra), Brit. Jr. Derm., 1930, xlii, 1–25; Trans. 8th Internat. Cong. Derm., Copenhagen, 1930, p. 886.
20. Percival, G. H., and Gibson, H. J.: Observations on etiology of erythema exudativum multiforme, Brit. Jr. Derm., 1931, xliii, 329–342.
21. Hallam, R., and Edington, J. W.: Investigation of alleged tuberculous etiology of erythema exudativum multiforme (Hebra), Brit. Jr. Derm., 1933, xlv, 133–141.

ATYPICAL HAY FEVER SEASONS; THEIR SIGNIFICANCE IN TREATMENT *

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It is now an accepted fact that specific and successful treatment of the hay fever patient presupposes a careful botanical investigation of the district in which the sufferer resides. Because of the marked variations in the flora of various parts of the country it has been necessary to make extended studies in many localities. While it cannot be said that the data which are at present available are entirely complete, nevertheless, we have information as to hay fever plants and pollen distribution in many representative sections of the country. The means used in surveying any locality consist of field observation and air analyses.[1] Field excursions conducted at various seasons of the year tell us of the kinds and quantity of probable hay fever plants and their seasons of pollination. The investigation of the air tells us the types of pollen capable of being transported by the wind, the scarcity or abundance of such pollens and the season for each particular variety of pollen.

The hay fever situation in any individual community has had to be studied further by observations on patients. Clinical tests have shown us that certain pollens, such as pine, although they may be present in the air in large numbers, fail to produce symptoms. Certain groups of plants characteristically produce very mild symptoms; certain others are well recognized as producing violent symptoms. The importance of some pollen-producing plants in some communities has been unduly minimized because of the small amount of pollen they have produced, or because of the almost complete absence of hay fever during their period of bloom.

Danger of Standardized Etiology

The correlation of the clinical and botanical data in any community has given us a rounded study upon which to formulate our ideas bearing on the causation and treatment of hay fever there. As a result of such studies in various localities there has naturally resulted the standardization of our etiologic and therapeutic concept in many places.

Increasing experience has taught us that in any locality such standardization, even though based on the average data obtained over a number of years of observation, may fail in unusual seasons. Unusual weather conditions may change the relative severity of the seasons and transform a plant ordinarily regarded as harmless into an important cause of hay fever. Of necessity it follows that if our treatment has been based entirely on the

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standard season we may be caught unawares and our therapeutic results will in some instances be disappointing. It is with the above idea in mind that we wish to call attention to the importance of considering in the management of our hay fever patient not only what the usual, but also what the atypical or unexpected season, may bring.

The 1934 hay fever season was atypical in many respects and in many parts of the country. We shall discuss somewhat in detail the unusual features of that season, particularly as it relates to the North Central states, and more specifically on data as gathered in Chicago and vicinity. It must be emphasized here again, however, that it is not our purpose to describe any local situation for the benefit of those locally interested but rather to illustrate some of the possible modifications which any year may bring in any place.

Typical Season in the Chicago Area

In the Chicago area, as in most parts of the North Central states,[2] especially east of the one hundredth meridian, there are three definite well-marked hay fever seasons caused by the pollens of the various trees, grasses, and the ragweeds. Tree pollens begin to appear in the air in quantity about the first of April and continue through May. The total amount of tree pollen in the air at any one time is not usually very great. Those trees which furnish the most of the pollen are oak, elm, poplar, the various maples, walnut and hickory. In spite of the fact that positive skin tests to tree pollens occur in a large percentage only a few persons have hay fever symptoms during April and the first part of May, and these are often interpreted as minor colds.[3]

The grass season begins in Chicago about the last week of May and lasts until the middle of July. The amount of grass pollen in the air during this time is never very great. This is probably due to the fact that grass pollens are all comparatively heavy. As a rule grass pollen is found to be much more toxic than any of the tree pollens, and a considerable number of people are sensitive to grass pollen only. Occasionally the symptoms are as severe as are ragweed hay fever symptoms.

Fall hay fever in Chicago appears any time after the first of August and continues through September. It is usually due to the pollen of ragweeds. Most persons who are sensitive to ragweed suffer severely unless protected by pollen treatment. The pollen content of the air as measured in the residence and business sections of Chicago during August and September is usually about 98 per cent ragweed, so that very little attention is ordinarily given to such possible offenders as Russian thistle, pigweed and lamb's quarters.

An Unusual Season in Chicago

During April and May 1934, the pollen content of the air was unusually high in the Chicago district. It seems reasonable to attribute the unusual amount of pollen from oaks, cottonwoods, elms, walnuts and other trees to

the ideal weather conditions during the pollinating season. Usually the pollination of the trees is much interrupted by frequent rains, each of which, of course, washes the pollen out of the air and interferes with that being matured on the trees. The hot dry weather this spring favored the ripening of pollen as well as its distribution. At this time the drought had not become severe enough to affect vegetation as deeply rooted as are the trees. Many patients who in past seasons had had very mild or no symptoms during the tree season but who showed skin sensitiveness to tree pollens, had definite and severe symptoms of hay fever this year.

TABLE I

Pollen Content of the Air in Chicago for Two Seasons

		1933		*1934*	
Trees					
	Maple	21		16	
	Elm	82		189	
	Oak	593		1078	
	Hazel	22		4	
	Alder	21		32	
	Pine	125		228	
	Poplar	44		41	
	Walnut and Hickory	35		145	
	Birch	24		148	
	Linden	2		2	
	Sycamore			18	
	Ash			12	
	Ailanthus			2	
	Willow			24	
	Hornbeam			2	
	Misc.	126		159	
			1095		2100
Grass					
	All species		370		82
Weeds					
	Red Sorrel	49		46	
	Chenopod	108		341	
	Composite	4		3	
	Hemp			2	
	Ragweed	7249		8625	
	Misc.	72		91	
			7482		9108
	Grand Total		8947		11290

Table 1 shows the marked increase in tree and chenopod pollens in Chicago during the 1934 season. The grass pollen production was reduced to a fraction of the average. The ragweed pollen count was unusually high.

The effect of dry weather on the grass pollen crop was just the opposite of that on the tree pollen crop. Grasses, on account of their shallow root system, respond very quickly to varying amounts of moisture. It is easy to see the beneficial effect of even a moderate shower when the grass is withered and dry. Thus, after a long period of dry weather, such as we had this spring, grasses are much damaged, and consequently, can mature only a small quantity of pollen. The total amount of grass pollen recorded in the

"loop" district of Chicago this spring was less than 15 per cent of what it has been for any of the previous three years. Grass hay fever was a rare affliction this season.

Evidently, the drought favored the growth of plants which thrive on less moisture than our common Chicago weeds. Russian thistle, lamb's quarters and other members of the goosefoot family broadcast three times as much pollen as usual. These plants have always been present in fair abundance in Chicago.[3] In some districts where the soil is favorable, Russian thistle is more common than any other weed. Some Chicago patients have given slight skin reactions and occasionally there has been a strong reaction to members of this family, but because of the relatively small output of pollen of this type, these reactions were seldom taken into consideration in therapy. This season, a number of patients began to have severe symptoms before ragweeds began to pollinate. On investigation it was found that these people were sensitive to Russian thistle and other chenopods and definite contact could be proved. The peak of the chenopod season occurred about nine days prior to the ragweed peak and it was not difficult to analyze the effect produced by the chenopods on the patients unprotected to it in spite of the fact that they were sensitive to both groups of pollens and that the two seasons overlap.

The Ragweed Season

In general, past experience seems to indicate that dry weather in June and July so retards ragweed development that the ragweed pollen crop may be predicted on much the same basis as a corn crop. On account of the drought this season, we felt confident that the fall hay fever season would be much less severe than usual, probably comparable to that of the drought year of 1930. Chicago had almost no rain during July, so on August 1 the giant ragweeds, then beginning to pollinate, were much below par, and short ragweeds were in many cases only a few inches high. One could hardly believe that rains beginning as late as the first week of August could so rejuvenate these stunted weeds that they would produce a normal crop. Giant ragweeds did not attain their usual growth but short ragweed responded like magic and, by the first week of September, was growing luxuriantly and producing abundantly.

Mild hay fever symptoms from ragweed began rather early, with severe symptoms occurring in most untreated cases by August 19. Counts on downtown slides as well as those exposed in the residence sections showed the apex of pollen contamination on September 4, which was the worst pollen day in Chicago since pollen record has been taken. The slide on the Post Office showed 1006 ragweed pollen per cubic yard. Severe concentrations continued until September 15 and toxic concentrations for another week. The total pollen count for the season was almost 20 per cent more than last year, and 70 per cent more than the average for the previous five seasons. Data from other parts of Illinois seem to show similar unusual

findings as were obtained in Chicago with respect to the pollens of trees, grasses, chenopods and ragweeds.

Frequent cool days resulted in many instances in a persistent nasal congestion, apparently due to a subacute inflammatory process, with resultant nasal obstruction but very little irritation, such as is shown by itching and sneezing. Sensitiveness to cold seemed to play a part in these patients. This has been observed in other seasons but, because of the cool days, has been more prominent this fall. Caution should be observed in advising hay fever patients to go to very cool places, refrigerators or on the water.

The rather frequent weather changes resulted in severe instances of asthma. It has been observed for a long time that the advent of asthma during the hay fever season is dependent on weather conditions more than on the pollen concentration.[4] Extreme weather changes such as rains, electrical storms, marked drops in temperature and marked barometric disturbances are prone to bring on attacks of asthma while the hay fever may be relieved. During the 1924 ragweed season we experienced an unusual amount of "bad weather"—many rainy days and frequent and great temperature fluctuations with the result that this season was one of the worst from the standpoint of asthma.

Comment

Apparently the standardization of what is usual for pollen production and hay fever symptoms in any locality may be disturbed by unusual weather conditions. The events in the Chicago area during the 1934 season would indicate to us that positive skin tests to tree and chenopod pollens (Russian thistle, lamb's quarters) should lead us to consider seriously treatment with such pollens in spite of the fact that the individual patient has usually had only minor symptoms caused by them. If such preseasonal treatment is not undertaken we should at least be ready to give coseasonal treatment with the appropriate pollen as soon as symptoms arise. The lesson to be learned applies, of course, to any district where the minor pollens are seldom considered in the treatment.

Another lesson to be learned from the above data is that prediction of the severity or date of onset of any part of the hay fever season is an extremely hazardous procedure, even if backed by many years of experience in the botany of hay fever. And finally, the recorded data of this year emphasize more than ever the importance of local botanical surveys and particularly the importance of counting and recording the varieties and amounts of atmospheric pollen for every day during every season.

REFERENCES

1. Koessler, K. K., and Durham, O. C.: A system for an intensive pollen survey, Jr. Am. Med. Assoc., 1926, lxxxvi, 1204–1209.
Huber, H. L.: Hay fever in the Chicago territory, Ill. Med. Jr., 1926, xlix, 133–138.
2. Feinberg, S. M.: Hay fever in the north central states, its causes and treatment, Ill. Med. Jr., 1932, lxi, 429–433.
3. Feinberg, S. M., and Durham, O. C.: Hay fever in Chicago and suburbs; clinical, field and air observations, Ill. Med. Jr., 1933, lxiii, 464–471.
4. Feinberg, S. M.: Allergy in general practice, 1934, Lea and Febiger, Philadelphia.

SENSORY CHANGES AND THE REFLEXES IN JUVENILE PARETIC NEUROSYPHILIS *

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BOTH the sensory changes and the reflex findings are of major diagnostic importance in juvenile paretic neurosyphilis. The present study, the fifth of a series of clinical studies of this disease, is concerned with the sensory changes including headaches, the status of the tendon and pathological reflexes, the temperature disturbances and the trophic changes in this disease. It is based on 43 personally studied cases and 610 cases reported in the literature.

SENSORY DISTURBANCES

Sensory disturbances in some form occur in juvenile general paresis in about 25 per cent of the cases, either as sensory skin changes, headaches, or leg pains. Their occurrence as reported in the 653 cases reviewed is as follows:

Headaches	74 cases	11.3 per cent
Leg pains	12 "	1.8 " "
Paresthesia	9 "	1.4 " "
Hyperesthesia	26 "	3.9 " "
Hypesthesia	53 "	8.1 " "

Headaches. Some form of headache occurring subsequent to the onset of the disease is reported in 11.3 per cent of the cases. Headache occurred in only four of my 43 cases (9.3 per cent). It has been previously stated that in some cases an acute severe headache appears as an epileptic equivalent, and in a few cases it is reported as following an epileptiform attack. The headache varies as to type, location, severity and duration. It is mentioned as a frequent prodromal symptom (Dahl [2]) and special notice is taken of headaches by Peterson,[11] in whose case they had been severe five months prior to other general symptoms.

Leg Pains. Cramp-like or lancinating pains in the legs are specifically mentioned only in 12 cases (1.8 per cent). Stewart [17] has emphasized the fact that although many cases of juvenile paresis present tabetic signs, there is a very infrequent occurrence of the leg pains so common to the acquired form of the disease, and quite frequently found in juvenile (congenital) tabes. They were not present in any of my cases, though often commented on by other authors. Arsimoles and Halberstadt [1] specially mention them; Köster [8] found special interest in the lancinating pains in his case; and they are recorded as present in cases reported by Alzheimer [22] (1895), Louvier [22] (1907), Trapet [22] (1909), Jelliffe [22] (1913), Schlicht [13] (1915), Klessens [22] (1917), Kupffender [22] (1918), Kleineberger [22] (1918), Fischer [22] (1921), and Masten [22] (1929).

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It is of special interest to find that of these 12 cases, five presented exaggerated knee jerks, in four they were absent, in two they were normal, and in the other their status is not stated. Thus the possible association of these pains with tabes is at least confusing in all but the cases showing absent knee jerks.

Paresthesia, Hyperesthesia, and Hypesthesia. Paresthesia is recorded in only nine cases, hyperesthesia in 26 cases (3.9 per cent), and hypesthesia in 53 cases (8.1 per cent). Schmidt-Kraepelin [14] reports six cases with regional hyperesthesia and 10 with hypesthesia. Weygandt [21] and Sänger [12] both mention a sensory disturbance in their cases, and Soukhanoff [16] reports an anesthesia present during labor. Halben's [5] case was a tabo-paretic.

As Kraepelin [9] points out, hypalgia appears always sooner or later in the acquired type of paresis. In the juvenile type because of the mental state it is often impossible to determine the presence of sensory changes accurately or even approximately. In some cases, the patient seems to be anesthetic; one of my patients repeatedly mutilated himself with sharp instruments and once clung to the radiator until his hands were severely burned (Case 2).[10] To interpret such action as hypesthesia might be justified, and yet it is not conclusive evidence of paretic sensory change. On the other hand, certain cases (particularly the far advanced cases with contractures) seemed invariably hypersensitive, even to gentle stimuli, which again is no conclusive evidence of hyperesthesia. Consequently, it seemed impossible in my own series to draw any accurate conclusions about sensory changes.

Changes in Reflexes

The status of one or more of the tendon reflexes was recorded in 531 of the 653 cases. Notation was also made of the cases in which a Babinski sign, clonus, Romberg's sign, and sphincter disturbances were present. The incidence of these is shown in the following table:

Reflex	Cases	Per cent of 653 Cases
Arm reflexes (biceps and triceps)		
Hyperactive	141	21.5
Normal	29	4.4
Diminished	3	.4
Absent	13	2.0
Knee jerks (quadriceps)		
Hyperactive	416	63.7
Normal	34	5.2
Diminished	19	2.9
Absent	62	9.4
Ankle jerk (gastrocnemius)		
Hyperactive	167	25.5
Normal	33	5.0
Diminished	13	2.0
Absent	35	5.3
Babinski sign present	97	13.7
Clonus (ankle)	74	11.3
Romberg sign present	44	7.7
Sphincter control disturbance	119	18.2

Tendon Reflexes. The table shows the frequency, as reported, of the hyperactive, normal, diminished, and absent tendon reflexes for the arm, knee jerk, and ankle jerk. The data regarding the status of the reflexes in the arm are sufficient only to note that an increase of these reflexes is the general rule.

Information regarding the status of the knee jerks is given in 531 cases. If the percentage of incidence of the various responses is based on these cases, we find that this reflex is increased in 78.3 per cent, normal in 6.4 per cent, diminished in 3.7 per cent, and absent in 11.6 per cent. The incidence in my own series of 43 cases is very similar: 81.4 per cent increased, 9.3 per cent normal, 4.6 per cent diminished, and 11.6 per cent absent. (These figures add to more than 100 per cent since in three cases the response was unilateral and was counted under both responses. In these three cases, it was absent on one knee while the other knee gave a normal response in one instance, and hyperactive in the other two.)

The results of other investigators closely parallel these figures: Dahl [2] found the knee jerks increased in 86 of 112 cases (76.8 per cent); Schmidt-Kraepelin [14] reports 90 per cent hyperactive and 7.5 per cent absent; Ferguson and Critchley [4] found 100 per cent (of 16 cases) hyperactive; Klauder and Solomon [7] report them present in "almost all the cases, but absent in a few."

As compared to the findings in the adult type of paresis (acquired), juvenile paresis shows a much higher frequency of exaggerated reflexes. Schmidt-Kraepelin [14] quotes Franz, who compiled his figures from 4,000 adults, as finding the knee jerk normal in 24.6 per cent, increased in 47.3 per cent, and absent in 28.1 per cent. Kraepelin [9] states that they are increased in two-third of the cases. Junius and Arndt [6] reported on the knee jerks in 992 cases; 16.3 per cent were normal, 54 per cent increased, and 29.6 per cent were diminished or absent.

Absent knee jerks were the finding in 11.6 per cent of cases (62 instances). This is a significant feature of juvenile paresis indicating posterior column involvement and the consequent association of the disease with tabes. Spinal cord involvement has been stressed by Junius and Arndt [6] in acquired paresis (they noted it in 29.6 per cent of their cases), and by Torkel [18] who found it in 16 per cent of 402 cases. Consequently we must conclude that 11.6 per cent of these cases reported as juvenile paresis, should be classed on the basis of their pathologic lesions as tabo-paresis. The inclusion of these cases as juvenile paresis is justifiable, however, since so far as can be determined, the other symptoms and signs predominately are paretic rather than tabetic. For the sake of pathological accuracy, Ferguson and Critchley [4] in their study of congenital neurosyphilis presented a separate group of tabo-paresis, including 12 cases, seven of which were so classified only because they showed absent knee jerks. As is shown in the present large series of cases, as well as in adult paresis, a small number persistently do show a late secondary involvement of the posterior columns of the cord.

Normal reflexes are of special interest and are reported here as occurring in 6.4 per cent of the 531 cases with the status of the knee jerks known. Schmidt-Kraepelin [14] found only one case in her 40 and there were three in my series and one additional which had a normal response on one knee and none on the other. The following case is of special interest, not only because the patient had normal knee jerks, but also was essentially negative on neurological examination. (It is very similar to the case reported by Toulouse and Marchand [19] with normal pupils and reflexes, and with typically paretic postmortem findings.)

*Case 15.** The patient was a negro, aged 17. His father was excessively alcoholic, and the mother was reported to be well, but none of the family were available for investigation. He did not walk or talk until his third year. He progressed in school to the sixth grade, and became employed as a grocery messenger after that time. He was committed to us after arrest on complaint of his employer because the boy claimed to have been robbed while taking money to a bank. *Physically* he was underdeveloped, with hypoplasia of the genitals. *Neurologically* on admission he showed normal pupils and reflexes, without gait disturbance or cranial nerve lesions. *Stigmata* besides his underdeveloped genitals, included a highly arched palate. *Mentally* he was childish, with very meager intellectual content, though oriented and coherent. He said he often heard God talking to him, but never gave details. Simple mental tests showed him entirely inadequate to give correct answers and often to even understand the questions. Basic mental age was five years. *Laboratory:* The blood and spinal fluid Wassermann tests were positive. *Course:* He was treated with mercury and after a temporary slight improvement was paroled for a short time, but returned. He developed marked paresis with ataxia and had to be confined to bed. He developed a marked tremor of his lips and tongue, and ataxic speech. No note was made at this stage as to the status of the pupils or reflexes, but with the spastic state, it is presumed they would have been increased. He deteriorated mentally, grew extremely weak, and died of an intercurrent infection at 19 years. The duration of symptoms was indefinitely estimated at two and a half years. No autopsy was obtained.

The ankle jerks in juvenile paresis are also generally increased, as indicated in the previous table; they are reported so in 25.5 per cent of the cases. In 35 cases (5.3 per cent) they were absent, and in these 35 cases, the knee jerks were hyperactive in seven cases, normal in one, and absent in the remaining 27 cases.

Babinski Sign (Dorsal Flexion of the Great Toe). The Babinski sign was present in 97, or 13.7 per cent, of the cases. Fairbanks [3] mentions that "they are occasionally elicited but are uncommon" (referring also to clonus), whereas the Babinski sign was present in 25.6 per cent of my own cases, and in 40 per cent of Schmidt-Kraepelin's [14] cases. Schlicht [13] and Kraepelin [9] also mention its frequent occurrence. Occasionally, there is a more or less permanent dorsal flexion of the big toe, a phenomenon often seen normally in infancy. The high incidence of the Babinski may also in some way be linked with its frequent occurrence in infancy and early childhood. There are no figures regarding its occurrence in adult paresis, but it is certainly less common than in the juvenile type.

* Cases 1 to 14 are included in the other papers of this series.

Clonus. Ankle clonus is reported as present in 74 cases (11.3 per cent). In my own series it was present in 11 cases (25.6 per cent), and was always associated with a marked spasticity and greatly exaggerated tendon reflexes. Schmidt-Kraepelin [14] reports one case where clonus was present in the hand.

Romberg Sign. This is reported present in 44 cases (7.7 per cent), although it was present in 20.9 per cent of my cases, all of which showed other evidences of ataxia. It was present in a fourth of the Schmidt-Kraepelin [14] cases which showed ataxia (and approximately half of mine). Fairbanks [3] makes the blunt statement that the Romberg sign "does not occur in this disease, at least in the child," which is certainly not in keeping with the facts just cited.

Sphincter Control. The loss of sphincter control is difficult to judge, since the patient often reaches the mental state when no attention is given to sphincter control, and as a consequence it is recorded as lost. Probably the actual nervous regulation of the sphincters rarely becomes disturbed, except with marked spinal cord involvement. Disturbance of sphincter control is reported in 119 cases in the entire series of 653 cases (18.2 per cent) and Ferguson and Critchley [4] report it in 62 per cent. Seventeen of my patients (39.5 per cent) were untidy so far as control of the sphincter function, but in none of these was there conclusive evidence of sufficient spinal cord involvement to cause a loss of sphincter control. In all, it might be truly said there was a loss of conscious control through mental deterioration, i.e. a cerebral loss of control.

Temperature Regulation

In none of my cases was there reported any conspicuous body temperature change except with an intercurrent infection just before death, or in association with extensive bed sores in bedridden patients with contractures. Schmidt-Kraepelin [14] noted some temperature fluctuations beyond the explanation of the apparent body state, but no hypothermia prior to death, as reported by Voisin,[20] and repeatedly observed in the adult form of paresis (Kraepelin [9]). Hyperthermia is occasionally present (Dahl [2]) without apparent explanation to be found on examination.

Trophic Changes

Trophic disturbances were not reported or apparent in any of my cases except in terminal bedridden cases in which the ulcers seemed to appear very easily and were not prevented even by the utmost care. I find no reference to such ulcers in Schmidt-Kraepelin's [14] report. Sebald [15] reports alopecia occurring in a case; and in one of Dahl's [2] cases there was a large pigmented hairy area covering the right scapula which was regarded as a stigmata rather than as having any association with the paretic process.

Summary and Conclusions

From a study of 610 cases of juvenile paretic neurosyphilis reported in the literature and of 43 personally observed cases the following conclusions may be drawn:

1. Sensory disturbances are present in some form in about 25 per cent of cases of juvenile paretic neurosyphilis.

2. Headache is reported in 11.3 per cent, and is to be regarded in some cases as an epileptic equivalent, occasionally as a prodromal symptom and nearly always as a consequence of the cerebral infectious process.

3. Leg pains of the tabetic type are exceedingly infrequent. They may be present even in the presence of hyperactive deep reflexes (i.e. without evidence of spinal cord involvement).

4. Hypesthesia is more than twice as common as hyperesthesia, though reliable evaluation of the presence of either seems questionable.

5. The knee jerks were hyperactive in 78.3 per cent, normal in 6.4 per cent, and diminished or absent in 15.3 per cent of cases. Cases with absent knee jerks must in most instances be regarded pathologically as taboparesis, although the predominance of paretic signs and symptoms justifies the inclusion of these cases in a study of juvenile paresis. The incidence of increased reflexes is much higher than in the adult (acquired) form of paresis.

6. The Babinski sign, indicating pyramidal tract involvement, was reported present in 13.7 per cent.

7. Clonus was present in 11.3 per cent.

8. The Romberg phenomenon was present in 7.7 per cent and is probably evident in about 25 per cent of all cases with marked ataxia.

9. Loss of sphincter control is frequently present, but usually represents a cerebral disturbance rather than any spinal cord involvement.

10. Body temperature disturbances are reported in only a very few instances, apparently much less frequently than in acquired paresis.

11. Trophic disturbances have not been reported.

BIBLIOGRAPHY

1. Arsimoles and Halberstadt: La paralysie générale juvénile, Ann. méd.-psychol., 1910, xi, 384–397; 1910, xii, 35–47, 239–250.
2. Dahl, W.: Über jugendliche progressive Paralyse, 1909, Inaug. Diss., Wurtzburg.
3. Fairbanks, A. W.: General paresis in childhood, Jr. Am. Med. Assoc., 1908, li, 1946–1954.
4. Ferguson, F. R., and Critchley, M.: Clinical study of congenital neurosyphilis, Brit. Jr. Child. Dis., 1930, xxvii, 1–14.
5. Halben, R.: Infantile Tabes resp. Taboparalyse bei einem 10 jährigen Mädchen, Deutsch. med. Wchnschr., 1909, xxxv, 1093–1094.
6. Junius, P., and Arndt, M.: Beiträge zur Statistik, Aetiologie, Symptomatologie, und pathologischen Anatomie der progressiven Paralyse, Arch. f. Psychiat., 1908, xliv, 249–305, 493–558, 971–1014.
7. Klauder, J. V., and Solomon, H. C.: Juvenile paresis with a presentation of 23 cases, Am. Jr. Med. Sci., 1923, clxvi, 545–558.

8. KÖSTER, G.: Zur klinik und pathologischen Anatomie der Tabes und Taboparalyse des Kindesalters, Monatschr. f. Psychiat. u. Neurol., 1905, xviii, 179–232.
9. KRAEPELIN, E.: General paralysis, 1913, Nervous and Mental Disease Monograph, New York, pp. 145–149.
10. MENNINGER, W. C.: Juvenile paretic neurosyphilis studies.
I. The incidence, sex, and age at onset, Am. Jr. Syph. and Neurol., 1934, xviii, 486–504.
II. Family history, with special consideration of familial neurosyphilis, Arch. Int. Med. (In press.)
III. The developmental history, including mental and physical growth, trauma and convulsions, Jr. Nerv. and Ment. Dis. (In press.)
IV. Cranial nerve and motor system syndromes, Arch. Neurol. and Psychiat. (In press.)
11. PETERSON, F.: Juvenile general paralysis, Med. Rec., 1913, lxxxiii, 1051.
12. SÄNGER: Case discussion, Neurol. Centralbl., 1905, xxiv, 1070.
13. SCHLICHT, J.: Causistische Beiträge zur Lehre von der juvenilen Paralyse, 1915, Inaug. Diss. München, C. Wolf and Sohn.
14. SCHMIDT-KRAEPELIN, T.: Über die juvenile Paralyse, 1920, Julius Springer, Berlin.
15. SEBALD, G. A.: Vier Fälle von progressiver Paralyse beim Kinde, 1917, Inaug. Diss. München, Kastner and Callwey.
16. SOUKHANOFF, S.: Paralysie générale et grossesse, Rev. de méd., 1903, xxiii, 554–560.
17. STEWART, R. M.: Juvenile types of general paralysis, Jr. Ment. Sci., 1933, lxxix, 602–613.
18. TORKEL, K. E. F.: Besteht eine gesetzmässige Verschiedenheit in Verlaufsart und Dauer der progressiven Paralyse nach dem Charakter der begleitenden Rückenmarksaffection, 1903, J. Hamel, Marburg.
19. TOULOUSE, E., and MARCHAND, L.: Paralysie générale juvénile et epilepsie, Ann. méd.-psychol., 1899, x, 281–291.
20. VOISIN, J., VOISIN, R., and RENDU, A.: Hypothermie prolongée a la période terminale d'un paralysie générale infantile, Bull. et. mêm. Soc. méd. d. hôp. d. Paris, 1906, xxiii, 905–911.
21. WEYGANDT: Über atypische juvenile Paralyse, Neurol. Centralbl., 1904, xxiii, 372.
22. To avoid unnecessary duplication, references of individual case reports will be given in a subsequent study.

BASOPHILIC ADENOMA OF THE PITUITARY;

REPORT OF A CASE OF "PITUITARY HYPERTENSION," TERMINATING IN CEREBRAL APOPLEXY *

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BASOPHILIC adenoma of the pituitary gland was described many years ago,[1] but it remained of restricted interest even to pathologists, the majority of whom have had little or no experience with the lesion. It will probably be seen with greater frequency as a result of Cushing's description of a well-defined associated syndrome.[2] This notable contribution was soon supplemented by equally stimulating papers by the same author on the questions of posterior lobe activity and its relationship to hypertension.[3] These and the studies of others [4] have served to focus attention on the pituitary as a probable factor in the development of hypertensive disease, and to emphasize anew the important rôle of that gland as the "motor of the body."

The absence (until recently) of a clinical correlation has obscured the importance of the basophilic adenoma. An excellent monograph [5] on the pituitary adenomata as late as 1925, dismissed the basophilic lesion with one line, stating that it was of no clinical importance. It is an intraglandular growth, situated in the anterior lobe. The few illustrations on record give one the impression that it is mostly situated anteriorly at or near the periphery (as it is in the following reported case), probably the result of the usual peripheral distribution of the basophilic cells. A curious and most important feature is that the adenoma is often so small that it escapes detection on gross examination and even on the routine histological inspection of one or two sections. It stands out in the stained section (hematoxylin-eosin) as a small, dark nodule, usually well circumscribed, but without definite encapsulation. The circumscription is caused by slight compression of the surrounding tissue, and in the instance here reported, by a rather prominent encircling lymphatic or sinusoidal network. Secondary nodules or a diffuse basophilic hyperplasia in the remainder of the anterior lobe may also be present. The adenoma is usually composed of large cells, often arranged in cords, showing in a general way some resemblance to the normal disposition of the pituitary chromophile cells. Only in one instance has an invasive tendency been reported; degeneration into a definite basophilic carcinoma has never been noted.[6]

The writer wishes to add another case report of basophilic adenoma, a good example of the syndrome described by Cushing. Unfortunately, this patient was in the hospital less than three days. Death ensued before adequate clinical studies were completed. The writer did not see the patient in

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life, but her appearance on the necropsy table was so striking that a tentative diagnosis of basophilic adenoma of the pituitary was made and verified by histologic examination.

Case Report

M.F., a white woman, aged 37 years, was admitted October 26, 1933 to the Medical Ward of the Jewish Hospital, on the service of Dr. Edwin Heller. During her evening meal, she suddenly felt dizzy, and gradually went into stupor. Examination in the hospital indicated a cerebral apoplexy involving the right internal capsule; she never recovered from coma. Eye examination revealed advanced hemorrhagic neuro-retinitis. The initial blood pressure reading was 220 systolic, 140 diastolic. It gradually fell to 100 systolic, 80 diastolic. The history obtained from the family was meager. The patient had attended the out-patient department of another hospital for one year, during which time she suffered headache and impaired vision, and was known to have had hypertension and diabetes; during the last month, the headache was intense. There had been no precordial pain, nor leg edema, but there was occasionally some dyspnea on exertion. She was unmarried, her menstrual history was unknown; the past medical history had apparently been uneventful.

Laboratory examinations were as follows: Urinalysis showed a specific gravity of 1.030, a light cloud of albumin, and no sugar. Granular and hyaline casts, and occasional erythrocytes were found. The blood count showed 4,600,000 erythrocytes, 20,100 leukocytes (86 per cent polymorphonuclear neutrophiles), and 84 per cent hemoglobin. The blood sugar was 186 mg. per 100 c.c. of blood, the blood urea nitrogen, 22 mg. The blood plasma CO_2 combining power was 60 per cent.

Death occurred on the third day of hospitalization.

Necropsy: The body was that of a middle aged, white woman, of medium stature, obese, with large shoulders, large trunk, and marked abdominal enlargement; the forearms, wrists, and ankles were small and narrow. There was a marked overgrowth of hair over the face and upper lip, the forearms, the thighs, and legs; over the scalp it was black and lustrous. The breasts were of moderate size and firm in consistency.

The supporting tissues were moderately dehydrated; the fat deposits, especially in the abdomen, were greatly in excess.

The heart was hypertrophied and weighed 480 gm. No vascular or valvular lesions were noted. The kidneys were of normal size and presented the grayish, putty colored cortex ascribed to nephrosis; they showed surprisingly little fibrosis in view of the clinical history. The adrenals were moderately enlarged and although the medullae showed autolysis, the cortical tissue was definitely hyperplastic and contained increased lipoid pigment. No adrenal tumor was noted. The thyroid was grossly normal. The ovaries were sclerotic and contained numerous small follicular cysts and a few corpora albicantes. The liver was grossly normal, but the pancreas appeared to be soft and presented numerous small foci of congestive softening in the body and tail.

The brain showed extensive hemorrhage into the ventricles and the right internal capsule was almost completely destroyed; the arteries over the base of the brain were moderately sclerotic. The pituitary was normal in shape and consistency, but slightly enlarged (10 by 8 by 6 mm.). Serial section was undertaken with the hope of finding a basophilic adenoma. In removing the pituitary it was noted that the dorsum sellae was extremely thin and that the bone was chipped away with ease. In this connection, it should be stated that marked brittleness of bone had also been noted on removing the breast plate.

Histology: The myocardium (left ventricle) shows a moderate hypertrophy. There is considerable albuminous swelling and fragmentation. Kidney: the renal capsule is moderately thickened. Most of the glomeruli are fairly well preserved;

many of them are swollen, but very few contain erythrocytes. Some are acutely necrotic with disintegrating capillary tufts. There is a striking tubular necrosis involving mostly the proximal convolutions. The small lobular arteries and arterioles are contracted, and have thickened walls which often are acutely degenerated (acute hyalinization of the media, edematous swelling and subendothelial lamellar fibrosis of the intima). Some small arteries also show an acute arteritis as evidenced by cellular and fibrinous infiltration within the walls, and many are completely blockaded by thrombosis. There is very little old interstitial scarring but there is considerable recent edematous and fibroblastic infiltration in areas where the tubular necrosis has been complete and is now undergoing resolution. The picture is that of an acute and subacute cortical degeneration due to arteriolar spasm and stenosis. The larger arteries are moderately thickened or contracted.

The adrenal section shows a prominent hyperplasia of the mid-cortical zone (zona fasiculata). The cells are large, pale staining, and the zone generally widened. In many areas, there appears to be a regenerative process in which nodular collections of cells are seen to be budding out, but no true adenomas are present. Many of these cells showed intense fatty degeneration. The zona glomerulosa is small; the inner (reticulata), moderately enlarged. The medulla is not seen.

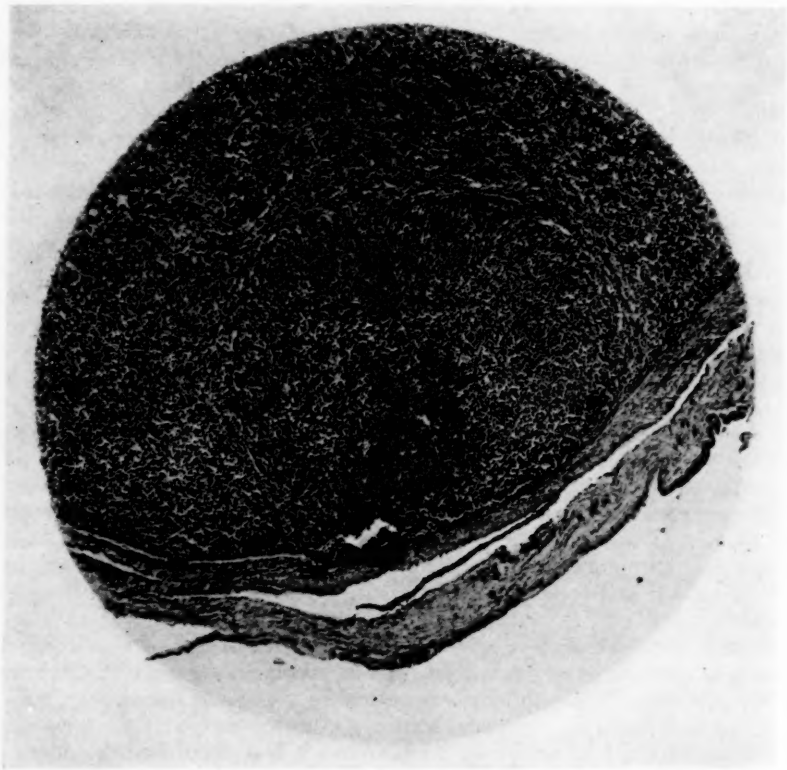

FIG. 1. Basophilic adenoma, anterior lobe (× 27). At the point of greatest cellular density, there is early invasion of the pituitary capsule.

The pancreas shows acute necrosis of many lobules. The islands share in the destructive process. There is an arteriolitis and marked contraction (spasm?) of the small arteries and secondary thrombosis, similar to that seen in the kidney. There is no true fat necrosis, but apparently ischemic necrosis.

The ovarian section shows a marked sclerosis, the presence of very few small primordial ova, and the absence of any medium sized or maturing follicles. There is one large follicle filled with degenerated granulosa cells. These findings suggest that normal cyclic development and ovarian stimulation were not present in this case. The thyroid and parathyroid were not sectioned. The liver presents a marked congestion and interstitial edema, and fatty degeneration.

In the lower anterior aspect of the pars distalis of the pituitary gland there is a small nodule, 2.5 by 2 mm., that takes the hematoxylin stain and stands out in definite contrast to the lighter stained remainder of the anterior lobe (figure 1). It is definitely circumscribed, separated from the surrounding tissue by rather large encircling sinusoids. The nodule is an adenoma composed of basophilic cells, smaller than the basophilic cells in the adjacent normal tissue; they are in alveolar and cord-like formations, closely aligned. In the central distal portion, the cells are densely packed and deeply stained. The adenoma reaches the pituitary capsule, and at one point, it has infiltrated through it, entering a large sinus in the outermost portion of the capsule (figure 2). The infiltrating cells apparently have been under great

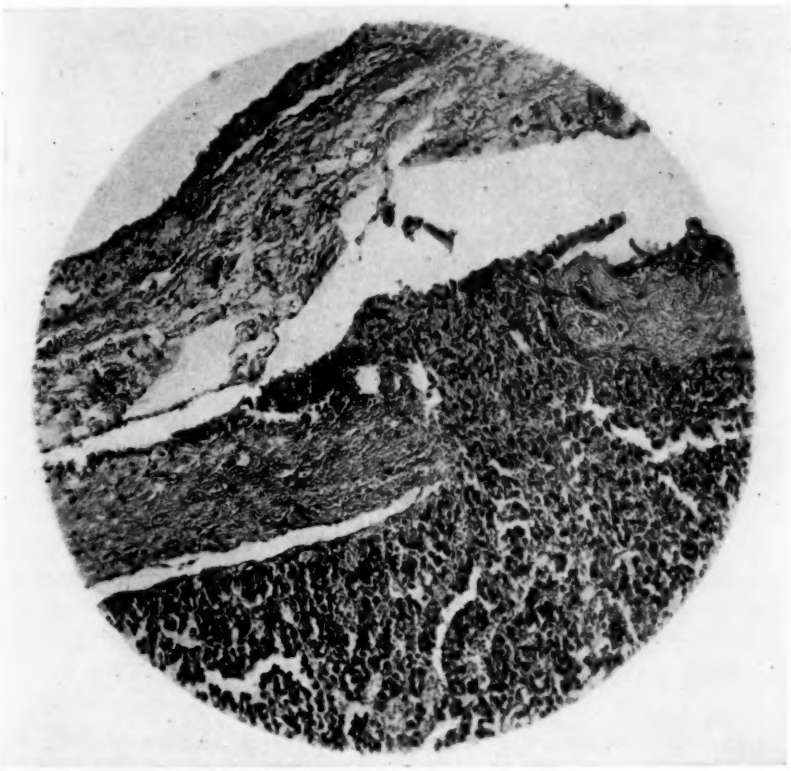

FIG. 2. Invasion through the pituitary capsule, into a large sinus (× 115).

pressure, being greatly compressed at this area. Many of them have practically fused together in their passage into the sinus, so that while the nuclei are more or less intact, the basophilic cytoplasm has some resemblance to a syncytium. Despite the evidence of rapid development of the adenoma, as suggested by the compression exerted on the surrounding glandular tissue, definite nuclear changes of carcinomatous development

are not seen. The invasion through the capsule, however, suggests a malignant tendency. Curiously enough, an occasional acidophile cell is seen in this basophilic adenoma, probably a result of early inclusion.

A small secondary basophilic nodule is seen nearby, consisting of cells of normal basophilic type and throughout the anterior lobe there is an increased basophilism. For a considerable number of serial sections, there is slight but definite invasion of basophilic cells into the pars nervosa (figure 3); and some of them have disintegrated

FIG. 3. Basophilic invasion of the pars nervosa (× 80).

here (apocrine secretion, indicative of posterior lobe activity, according to Cushing). Section of the stalk shows marked congestion of the hypophysio-portal vessels, but all the pituitary vessels, especially the sinusoids within the anterior lobe, are heavily congested.

DISCUSSION

This patient presented the characteristic physical changes that lately have been linked to basophilic pituitary adenoma. The face was large and broad, and coarse featured; the eyebrows were unusually heavy and bushy and there was a marked hirsuties. The face had apparently not been shaved in the last few days of life and the hair growth was prominent. The large trunk, especially the abdominal enlargement, was in sharp contrast to the narrow forearms, wrists, and feet. Purplish striae were not seen, possibly because they were not looked for.

The clinical aspect of malignant hypertension (the comparatively youthful age level, the rapid course, and the presence of advanced hemorrhagic neuro-retinitis) was corroborated by the presence of severe arteriolar degeneration in the kidneys, accompanied by an acute and subacute degeneration of the parenchyma. The renal changes of malignant hypertension found in cases of basophilic adenoma are discussed in a paper recently published by MacMahon.[11] Hypertension has been noted in practically every case of basophilic adenoma. This constant association, and the recent investigations of Anselmino in eclampsia make it appear that pituitary activity and hypertension are much more than coincidental. Pituitary basophilism was noted some years ago in association with glomerulo-nephritis, nephrosclerosis and uremia. Unfortunately there was no correlated study of the pituitary gland in the earlier stages of the hypertension that must have preceded those late features of "renal-vascular" disease.

Adrenal hyperplasia has been considered in many quarters to be the primary factor in the pathogenesis of hypertension. Until the work of Cushing, this patient in all probability would have been regarded as suffering from hyperadrenalism or possibly the "diabete hirsute" of the French. There is a well-recognized syndrome of primary hyperadrenalism usually seen as the result of a neoplastic process in the adrenal cortex. It is featured by hypertension and often by virilism. In the light of the recent knowledge of the pituitary adenomas, one wonders what serial section of the pituitary gland would reveal in such cases. Marked secondary changes are now known to occur in the endocrine system as a result of pituitary activity; the adrenals may become hyperplastic, even to the point of development of small cortical adenomas. In this case the mid-cortical zone was definitely hyperplastic (2.5 to 3 mm. thick) and heavily infiltrated by lipoid substance. Incidentally, the polycythemia seen in some patients with basophilic adenoma, but absent in this case, has been attributed to adrenal stimulation.[7]

The cases of basophilic adenoma previously reported usually presented diabetes mellitus in what might be called a capricious form, often not amenable to insulin and often characterized by waves of exacerbation and regression. The meager history obtained in our case suggested the existence of such a diabetes. The patient had been attending the diabetic clinic in another hospital for almost one year, and was there regarded as having diabetes; she apparently had received no insulin.

The thymus was atrophied; the ovaries were cystic and sclerotic; the thyroid was of normal size and consistency. In this state of pituitary basophilism the thyroid is usually inactive and often small. Sections for histologic study were either lost or not cut; also in the press of time and in the concentration of our attention on the pituitary gland, the removal of the parathyroid glandules was neglected; there was nothing in the gross appearance that suggested growth or undue hyperplasia. In previous case reports, with one possible exception,[8] no primary neoplasm of the para-

thyroids was found, although decalcification was occasionally the outstanding clinico-pathological feature. As already stated, abnormal decalcification was noted in this patient; the dorsum sellae was chipped away as if it were made of the thinnest paper-like shell. Decalcification in this structure was noted both in the roentgenologic and in the necropsy examinations in the cases of Parkes-Weber [9] and Turney.[10]

The pituitary gland was slightly enlarged, but of normal shape; in fact, the gross appearance of the gland was disappointingly normal, and this reemphasizes the need for serial section in a case that clinically suggests the presence of basophilic pituitarism. It explains the failure of distinguished continental pathologists to discover the basis of the peculiar syndrome after they had examined the pituitary; it also accounts for the negative pituitary findings of brain surgeons in operations on patients who probably did have basophilic hypophyseal adenoma. One marvels that such a small lesion could be of such importance. It was found by Parkes-Weber [9] in a typical example of the now recognized associated syndrome, but at that time he refused to believe that it could possibly give rise to such remarkable systemic effects. In the series of 14 proved cases tabulated by Cushing, only two or three achieved such macroscopic enlargement as to be able to cause the local pressure changes usually attributable to pituitary neoplasms and cysts.

In this patient, the pituitary gland showed of course, as its main structural change, the basophilic adenoma; but two other features deserve special comment.

Histologic examination showed a slight, but definite, basophilic invasion, from the anterior lobe into the pars nervosa. While this was slight, in contrast to the considerable invasion reported by Cushing, it was extant for a considerable distance along the border of the pars nervosa, being noted in a fairly large number of serial sections. Cushing believes that basophilic invasion activates the pars nervosa so that the pressor function of that lobe is accentuated. More specifically he believes that the basophilic cells disintegrate on invasion into the pars nervosa, in the process of an apocrine secretion; that the products thus formed, eventually find their way into the hypothalamus, the infundibular canal and the third ventricle; and that excessive infiltration of this type is the pathological basis of the hypertensive states such as eclampsia and essential hypertension.[12] This attractive theory of course must stand the acid test of time; if it does so and becomes an established fact, the study of the development of pituitary basophilism and the manner of access of the basophilic products to the systemic circulation, will obviously be of the utmost importance.

The second histologic feature in this case may, therefore, be of more than casual interest; this adenoma although structurally not carcinomatous had forced its way into a large vascular space which evidently was a sinus (a branch of a cerebral venous sinus) within the pituitary capsule. It was a matter of discussion as to whether this channel was a real blood sinus or an

unusually large lymphatic space. It was lined by delicate vascular endothelium and contained some blood cells; at any rate, there was indication of rapid anatomical invasion and the injection into the systemic circulation of possibly large amounts of the secretion of a hyperplastic ductless gland.

Summary

On the basis of certain physical characteristics, and structural changes, in a woman aged 37, a tentative necropsy diagnosis of basophilic hypophyseal adenoma was made and verified by serial histologic section. The clinical history indicated the presence of diabetes mellitus and the malignant form of hypertensive disease. In this connection, there was interesting histologic evidence of severe and relatively acute arteriolar disease in the kidneys and to a lesser degree in the pancreas. The pituitary adenoma, although small, had invaded a large sinus within the pituitary capsule.

The writer is indebted to Dr. Harvey Cushing, Dr. Louise Eisenhardt, and Dr. H. E. MacMahon for their examination of the microscopic sections, and to Dr. Edwin Heller for the privilege of reporting this case.

BIBLIOGRAPHY

1. Erdheim, J.: Über das eosinophile und basophile Hypophysenadenom, Frankf. Ztschr. f. Path., 1910, iv, 70–86.
2. Cushing, H.: Basophile adenomas of pituitary body, and their clinical manifestations (pituitary basophilism), Bull. Johns Hopkins Hosp., 1932, l, 137–195.
3. Cushing, H.: Posterior pituitary activity from anatomical standpoint, Am. Jr. Path., 1933, ix, 539–548.
4. Anselmino, K. J., Hoffmann, F., and Kennedy, W. P.: Relation of hyperfunction of posterior lobe of hypophysis to eclampsia and nephropathy of pregnancy, Edinburgh Med. Jr., 1932, xxxix, 376–388.
5. Dott, N. M., Bailey, P., and Cushing, H.: Hypophyseal adenomata, British Jr. Surg., 1925, xiii, 314–366.
6. Ewing, J.: Neoplastic diseases, 3 Ed., 1928, W. B. Saunders Co., Philadelphia.
7. Moehlig, R. C., and Bates, G. S.: Influence of pituitary gland on erythrocyte formation, Arch. Int. Med., 1933, li, 207–235.
8. Schmorl, G.: Zur Geschichte der Plazentarzellenembolie, München. med. Wchnschr., 1912, lix, 2111.
9. Parkes-Weber, F.: Cutaneous striae, purpura, high blood pressure, amenorrhea, and obesity of the type sometimes connected with cortical tumors of the adrenal glands, occurring in the absence of any such tumor, British Jr. Dermat., 1926, xxxviii, 1.
10. Turney, H. G.: Discussion on disease of the pituitary body, Proc. Roy. Soc. Med. (Sections of Neurology and Ophthalmology), 1913, pages lxix-xciv.
11. MacMahon, H. E., Close, H. G., and Hass, G. M.: Cardiovascular renal changes associated with basophile adenoma of anterior lobe of pituitary (Cushing's syndrome), Am. Jr. Path., 1934, x, 177–191.
12. Cushing, H.: Hyperactivation of neurohypophysis as pathological basis of eclampsia and other hypertensive states, Am. Jr. Path., 1934, x, 145–176.

ARTIFICIAL PNEUMOTHORAX THERAPY *

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The most extensively used and the most successful procedure of compression therapy in the treatment of pulmonary tuberculosis is artificial pneumothorax. Other procedures of compression or collapse therapy should be used when pneumothorax is impossible, unsuccessful, or when indicated as an adjunct to the compression and relaxation obtained by pneumothorax induction.

When the tuberculous involvement is apparently limited to one lung and is of a character considered of sufficient clinical significance, unilateral pneumothorax is indicated. When this character of involvement exists in both lungs, bilateral pneumothorax is indicated.

In treating a large group of cases by this type of therapy, certain difficulties will be encountered which may preclude the induction of pneumothorax or at best the pneumothorax will be unsatisfactory. Through success, partial success or failure, the series of cases selected for this particular type of compression therapy will be automatically subdivided in the following case groups:

1. Unilateral pneumothorax with hemidiaphragmatic paralysis.
2. Pneumothorax with contralateral hemidiaphragmatic paralysis.
3. Bilateral pneumothorax.
4. Thoracoplasty with contralateral pneumothorax.

The size of these case groups should be as in the order named. All therapeutic pneumothoraces should be instituted very gradually, increasing the degree of compression until the desired amount is obtained. When the necessary compression is obtained, it should be maintained by frequent small refills, sufficient to maintain the desired area in a relatively static compression state and yet allow relatively uninvolved portions partially to reëxpand. Carefully induced and carefully maintained collapse produces an expansile type of pneumothorax which not only greatly lessens the development of complication but aids in accomplishing reëxpansion of the treated lung at the termination of the therapy. Each case should be conducted individually, carefully judging lung compression and need of compression by frequent fluoroscopy. No case should receive a pneumothorax refill without fluoroscopic observation immediately preceding the refill. It is believed that fluoroscopy after each refill is a worthwhile observation.

To conduct pneumothoraces properly, the attending physician must constantly consider the individual's precompression pulmonary disease with special consideration of the initial amount and type of disease when pul-

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monary reëxpansion is contemplated. This consideration must of necessity involve a detailed study of parenchymal infiltration and pulmonary cavities as to extent, character and location.

Consideration of these factors is of great aid in determining the duration of the therapy. Pneumothorax therapy is terminated when there is definite disease arrest over a satisfactory period. Disease arrest is determined by an accurate estimate of the patient's clinical status and this estimate is made from a composite picture of all clinical data available. In this estimation, great importance is attached to roentgen-ray interpretation and since the problem of determining an accurate clinical status is a problem of the clinician, he should be the one who makes the interpretation of the roentgen-ray film. Serial roentgen-ray films are our greatest aid in observing pulmonary changes incident to compression therapy.

The opinions just enumerated are well known to all phthisiologists. The value of artificial pneumothorax therapy is so well established that the procedure is seldom discussed in the current medical literature. Discussion of the subject, however, is warranted because suitable cases for pneumothorax treatment exist in all sanatoria, yet are under a régime of ordinary rest treatment. The procedure is not employed nearly so extensively as it should be, as too many suitable cases are on rest régime and will remain so until disease progression or some emergency demands the induction of pneumothorax. During periods of unwarranted delay, these patients are subjected to the potential dangers of hemorrhage and bronchogenic spread of the disease. Since, in most instances, pleural involvement is a part of the tuberculous process, a continuation of pleural apposition will often result in new formed pleuro-pulmonary adhesions or even in pleural symphysis. In many instances, a delay ends not only in disease progression but by pleural changes; and through these latter the patient is denied the advantage of the most powerful weapon to combat the progression of pulmonary tuberculosis.

The success of unilateral artificial pneumothorax therapy is well established and a discussion of results obtained would serve no particular purpose. We believe, however, that in many instances this most useful therapy is either much delayed or even denied the patient through fear of attendant complications. It is my belief, however, that the unfavorable potentialities of an active pulmonary tuberculous process are to be feared far more than those of an induced pneumothorax.

We have studied and accurately tabulated the various complications in 700 pneumothoraces induced and conducted on one of the tuberculosis units at Fitzsimons Hospital. Presentation of these data may tend to help allay apprehension in regard to the use of this valuable procedure of compression therapy.

Hydropneumothorax of clinical significance occurred in 34.5 per cent of cases, pyopneumothorax in 5.8 per cent, superimposed spontaneous pneumothorax in 13.7 per cent, air embolism in 0.57 per cent. Mortality from complications has, in the main, resulted directly or indirectly from superimposed

spontaneous pneumothorax; directly because of a large patent pleuro-pulmonary fistula, indirectly because of subsequent development of pyopneumothorax. There were no deaths from air embolism in this series of 700 cases.

Unilateral Pneumothorax with Hemidiaphragmatic Paralysis. We have found pleuro-pulmonary adhesions to be an etiologic factor in the development of complications in pneumothorax therapy. We have concluded that hemidiaphragmatic paralysis decreases the tension upon pleural adhesions which lessens the probability of certain complications. It was noted in the beginning, when the various classes of pneumothoraces were enumerated, that unilateral pneumothorax included the adjunct of hemidiaphragmatic paralysis. This was done for the following reasons:

1. Hemidiaphragmatic paralysis is of value as a supplement to artificial pneumothorax therapy when additional compression and relaxation are required for cavity obliteration because of pleuro-pulmonary adhesions.

2. Artificial pneumothorax complicated by acute pleuritis with or without serous exudation may tend toward obliteration of the pneumothorax space. Untimely obliterative pneumothorax may end in disease progression unless some procedure of compression therapy is substituted for the pneumothorax. We advocate that this procedure be hemidiaphragmatic paralysis.

3. Upon completion of a successful pneumothorax, paralysis of the hemidiaphragm is indicated as a preëxpansion procedure. Diaphragmatic elevation decreases the size of the hemithorax and this diminishes the degree of pulmonary reëxpansion required, decreases or prevents mediastinal retraction and causes permanent continuation of some compression and relaxation. There is also the safety factor of some decrease in pulmonary function.

4. It is indicated as an adjunct when the pneumothorax is unsatisfactory because of partial pleural symphysis.

5. When artificial pneumothorax, after a sufficient period, fails to obliterate midlung cavities, hemidiaphragmatic paralysis is indicated.

We have concluded that paralysis of the hemidiaphragm is of value when certain factors tend to make the artificial pneumothorax unsatisfactory and when, though the pneumothorax therapy has been successful, pulmonary reëxpansion is contemplated. Since it is of value under unfavorable conditions and since it is advocated as a preëxpansion procedure, we see no reason why practically all cases of artificial pneumothorax should not have the advantage of hemidiaphragmatic paralysis.

Artificial Pneumothorax with Contralateral Hemidiaphragmatic Paralysis

In bilateral active pulmonary tuberculosis, contralateral phrenic exeresis is indicated under the following conditions:

1. When pneumothorax is impossible on one side.

2. When pneumothorax does not produce the desired pulmonary compression.

3. As the procedure of choice when the character and distribution of lesions are such as to promise favorable results by hemidiaphragmatic paralysis.

In moderate or far advanced pulmonary tuberculosis, one of the chief difficulties of utilizing bilateral compression by induced pneumothorax is that of extensive pleuro-pulmonary adhesions or pleural symphysis, complete or partial. Attempts to induce pneumothorax fail or at best yield unsatisfactory results. Paralysis of the hemidiaphragm is then induced as a suitable procedure of pulmonary compression. This measure may be instituted with a view of obtaining the desired result or used merely in an attempt to control disease progression during the interval of bringing under control the tuberculous lesions of the opposite side. If the latter problem is the situation, it may be necessary later to perform thoracoplasty upon the hemithorax presenting pleural symphysis.

In other patients in whom a successful pneumothorax has been induced upon the more involved side, the type and distribution of the lesions of the contralateral lung may be such as to be controlled by hemidiaphragmatic paralysis. In other words, it is estimated that it will be unnecessary to induce a bilateral pneumothorax and, instead, the less radical procedure of phrenic exeresis is at least given a trial for a satisfactory period. In the event that the desired results are not obtained, some other more drastic procedure may then be attempted.

Phrenic exeresis with its subsequent diaphragmatic paralysis, elevation and immobilization, often yields excellent results when applied to properly selected cases. In other instances, though disease arrest is not accomplished, the desired aim of the procedure is obtained. The success of any compression procedure is established if it really accomplishes the clinician's intended aim. Phrenic exeresis has doubtless suffered somewhat as to its reputation as a curative compression procedure because of instances of its wholesale application in the treatment of pulmonary tuberculosis. Any method of therapy meets with success only when applied with reasonable discrimination.

Paralysis of the hemidiaphragm in properly selected cases often produces excellent results, even when used as the sole measure of pulmonary compression. This measure is capable of preventing disease progression in one lung during the interval of pneumothorax therapy on the opposite side. This course of action may be essential prior to the induction of radical chest surgery.

Bilateral Pneumothorax

In treating any large series of cases of pulmonary tuberculosis, one encounters many patients in whom the application of unilateral compression therapy procedures is precluded because of extensive bilateral disease. In this group, bilateral pneumothorax should be attempted and when difficulties hinder or prevent its successful employment, other measures of compression or collapse therapy should be instituted.

In discussing unilateral pneumothorax, most phthisiologists advocate its use on the basis of their inability to obtain and maintain disease arrest by the so-called " rest cure." If they doubt their ability to treat tuberculosis satisfactorily when the disease process is relatively confined to one lung, how can one expect to accomplish results by this method when the disease process is definitely bilateral? If unilateral pneumothorax is indicated in relatively unilateral tuberculosis, it is believed that bilateral pneumothorax is urgently needed when an active disease process involves both lungs.

Frequently patients are advised that they are unsuitable subjects for artificial pneumothorax therapy because the contralateral lung presents active involvement entirely too extensive to withstand compression of the more involved side. The patient is advised to undergo routine rest treatment with a view of improving the better side sufficiently to warrant the induction of unilateral pneumothorax. In instances, this procedure may yield satisfactory results but in the majority of instances, the interval of delay allows disease progression sufficient to preclude the induction of unilateral compression. Delay subjects the patient to all the potential dangers of active tuberculosis or of cavitation which are so often stressed in unilateral tuberculosis and which are even more imminent in bilateral disease.

Results from bilateral pneumothorax are not as excellent as those usually obtained from the unilateral procedure. We must bear in mind, however, that we are dealing with patients presenting far advanced tuberculosis in whom the tuberculo-immune qualities may be depressed. These patients are generally those who have suffered a more or less severe bronchogenic spread from the older involved lung to the contralateral lung. Often it is this recent disease extension that brings the case initially to the sanatorium. In other instances the extension occurs in cases of long standing that have been trying to " carry on " in spite of chronic pulmonary tuberculosis. Due to the fact that the disease process is frequently of long standing in one lung, it is difficult because of pleuro-pulmonary adhesions or pleural symphysis to induce a satisfactory pneumothorax. Complications encountered in conducting bilateral pneumothorax are frequent and often severe but in considering this fact we must again consider that we are dealing with cases of far advanced tuberculosis with, in most instances, a hopeless prognosis if untreated. In considering the possibility of complications, one should remember that in far advanced tuberculosis untreated by compression therapy, certain extra-pulmonary tuberculous complications such as laryngitis or enterocolitis may soon make their appearance, possessing a gravity far outweighing the usual complications of bilateral pneumothorax. Extensive bilateral disease demands immediate compression treatment and the application of this therapy should be carried out with great care.

We have induced and carried on bilateral pneumothorax in 93 cases of bilateral pulmonary tuberculosis. Many of these cases have not been completed and end results cannot be reported. May it suffice to state that results have been very gratifying and we enthusiastically advocate the procedure.

In 1931, after a careful analysis of 25 cases treated by bilateral pneumothorax, we recorded the following conclusions:

1. Advanced bilateral pulmonary tuberculosis may be arrested by bilateral pneumothorax.
2. Bilateral cavitation may be eradicated.
3. A rapid fatal termination from bronchogenic spread to the contralateral lung may be prevented by converting the case from a unilateral to a bilateral pneumothorax.
4. Bilateral pneumothorax, even when unsatisfactory on one or the other side, may cause sufficient improvement to warrant the utilization of surgical collapse previously precluded because of extensive bilateral disease.

After three more years of experience with bilateral pneumothorax we do not wish substantially to alter these conclusions.

Thoracoplasty in the Presence of Contralateral Pneumothorax

In cases of bilateral pulmonary tuberculosis, the induction of artificial pneumothorax may be impossible or at best unsatisfactory on the more massively involved side because of complete pleural symphysis or a pleural symphysis over the involved area. The lesser involved side may present sufficient involvement to preclude radical surgical collapse contralaterally. This group has been successfully treated by first inducing pneumothorax for compression of the better lung and when compression is well established and maintained by weekly refills, a thoracoplasty is performed on the massively involved side. In the event that it seems advisable to delay the institution of surgical collapse, a hemidiaphragmatic paralysis is performed to maintain in a quiescent state or to improve the tuberculous process during the interval of delay. Phrenic exeresis is not routinely performed in these cases since in some instances it may be advisable to conserve pulmonary function.

We have performed thoracoplasty in the presence of contralateral pneumothorax in 11 cases and have instituted contralateral pneumothorax in another case shortly after thoracoplasty. Excellent results have been obtained in this small series of cases as 11 cases are living in a group of 12 cases where the prognosis, without bilateral compression therapy, seemed hopeless. One case died several months after thoracoplasty, of disease other than tuberculosis.

It is interesting to note that all of these cases endured major chest surgery extremely well. When thoracoplasty is performed in the presence of contralateral pneumothorax, we have done so in the presence of a reduced contralateral pulmonary compression and this compression has been maintained in a reduced status during the postoperative convalescence. In these cases, it is essential that the extent of rib resection be cautiously estimated, limiting the operation according to the patient's ability to withstand the operative procedure. Four of our cases had their thoracoplasty performed in two stages and eight cases were operated on in one stage.

In cases requiring bilateral compression therapy where it becomes neces-

sary to perform thoracoplasty, it seems of extreme importance thoroughly to collapse the involved area and to leave as much functioning pulmonary tissue as possible. This is accomplished by subtotal costotectomy over the involved area. In bilateral pulmonary tuberculosis where pneumothorax cannot be induced with success on the more involved side, thoracoplasty may be performed with success when the disease of the contralateral lung is under control by artificial pneumothorax.

In conclusion, we believe that the evolution of artificial pneumothorax therapy has resulted in its greatly increased applicability. Groups of cases, as enumerated above in which pneumothorax has been successfully employed, clearly demonstrate the scope of its present day usefulness. A decade ago, certain indications for the use of pneumothorax, now confirmed by successful application, would have seemed radical, probably too radical. For instance, the use of pneumothorax contralaterally in the presence of thoracoplasty might have been condemned by some of the prominent phthisiologists. The progress in pneumothorax therapy has been of a very creditable character and the workers who have contributed to this progress have added much to the control and treatment of pulmonary tuberculosis.

CLOSED INTRAPLEURAL PNEUMOLYSIS *

By James H. Forsee, M.D., *Denver, Colorado*

The marked progress which is steadily being made in the surgical treatment of pulmonary tuberculosis demands that we frequently report the progress achieved by any particular procedure of compression therapy. Such a report must include not only a description of any improvement in operative technic but also recommendations regarding the selection of cases with an accurate survey of the results obtained by the particular method. The particular procedure to be discussed in this paper is closed intrapleural pneumolysis utilizing the electro-surgical method. The report is based upon my experience in 30 thoracoscopies with the cauterization of adhesions in most instances. The cases herein described, however, include only the 17 operated upon by the electrosurgical method between the periods July 1, 1931, and March 1934. They illustrate the results which may be obtained when properly selected cases are placed under the care of one competent and properly equipped to perform the Jacobaeus operation.

Intrapleural pneumolysis is an operative procedure for severing adhesions, extending between the parietal and visceral pleurae, which prevent satisfactory collapse of the affected lung. The closed method, as originally presented by Jacobaeus in 1913 and later modified by Unverricht and Matson, is the operation of choice. We have found the incidence of this operative requirement during the past five years to be approximately 5 per cent of all our artificially induced pneumothoraces. More recently this percentage has been decreased due largely to our adoption of phrenic exeresis as an integral part of pneumothorax therapy. However, in some cases phrenic avulsion may be contraindicated, and when adhesions prevent collapse a lung cavity may remain patent in which instance the Jacobaeus operation becomes mandatory. An appreciation of results obtained may be gathered from Moore's recent exhaustive survey of the literature in which he collected 1850 cases reported by 45 different authors.[1] Of these, 75.5 per cent were clinically successful. The operative mortality was 1.08 per cent and 4.5 per cent were made worse by the operation. When compared with 52 collected cases of open pneumolysis, these results are far superior to the latter operative method. In the open type of operation, the operative mortality was 19.2 per cent with a like percentage of cases made worse by operation and only 57.6 per cent were clinically successful. Consideration of these figures makes further comparison unnecessary especially under present operative methods.

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From the Medical Service, Fitzsimons General Hospital, Denver, Colo.

Indications

The operative indications include those for thoracoscopy and those for cauterization at the thorascopic examination. The difference is fundamental in that the indications for cauterization are entirely dependent upon the thoracoscopic findings. Results will, to a very appreciable degree, depend upon the experience and judgment exercised in the selection of adhesions for cauterization at thoracoscopy. Broadly speaking, we believe that regardless of location, thoracoscopy is indicated in all cases under pneumothorax therapy with unsatisfactory pulmonary compression over the diseased areas because of pleural adhesions, when the unsatisfactory compression is not obviously due to adherent lung tissue. Whether or not an attempt is made to cut offending adhesions is determined by intrathoracic inspection.

Contraindications

We have recognized no contraindications to thoracoscopy if the indications just enumerated are present. The presence of a bilateral pneumothorax only makes it more urgent. The presence of a virulent pyopneumothorax would contraindicate cauterization and therefore thoracoscopy would be unnecessary; however, a chronic purulent exudate, in an afebrile patient, is not a contraindication. The tuberculous disease may be so extensive that little hope for recovery exists even though the adhesions be severed, and in such cases thoracoscopy is not warranted. Since thoracoscopy is essentially free from danger, each case must be adjudged on its own merits and the patient given the benefit of the procedure, provided that the operator does not attempt such impossible tasks that his inevitable poor results bring the procedure into disfavor. Unwise selection of cases for cauterization should result in criticism of the operator rather than in condemnation of the surgical procedure.

Selection of Cases

The operator should be competent to select the cases for operation. He should be trained in phthisiology, experienced in pneumothorax therapy and a competent surgeon. At present, few possess such qualifications, and cases are selected by the coöperation of the phthisiologist, roentgenologist and surgeon. Careful evaluation of the clinical course of the disease together with meticulous study of serial roentgenograms before and during the course of pneumothorax therapy is essential. A word of caution is necessary; operability cannot be determined on roentgenographic study alone as it is impossible from a study of the films to determine accurately the number, width, or thickness of adhesions; one cannot determine whether only the edge or entire width of the adhesion is shown. At times it is questionable whether we are dealing with adhesions or adherent lung, or to what extent both are present. The adhesions are more numerous and generally larger than they appear on the film. Thus, roentgenographic study is of value in

selecting cases for thoracoscopy and as an aid in determining the site for introduction of the thoracoscope but decision regarding cauterization can be made only by inspection of the adhesions through the thoracoscope.

Technic

The technic which we have found most valuable and have used during the past three years is the electrosurgical method as presented by Matson.[2] The advantages of this method are: First, with more adequate coagulation it is possible to prevent or control hemorrhage. Second, less heat and smoke are produced, decreasing the extent of tissue reaction at the site of cauterization. Third, postoperative complications are decreased. Fourth, manipulation of the electrode within the thorax is less difficult than is the handling of the rigid cautery.

Partial Cauterization of Adhesions

It has generally been understood that the offending adhesions are completely severed at operation; while this is desirable, it is often impossible and at times unnecessary. Our experience has shown that the partial or incomplete cauterization of the larger adhesions is often followed by the closure of the cavity under continued pneumothorax therapy. Repeated operations may be necessary; however, a satisfactory pneumothorax may result from a single partial cauterization. String, cord-like or fan-shaped adhesions, and small bands often interfere with the pulmonary compression but fortunately offer few operative difficulties. Funnel-shaped or diffuse fold adhesions, and large bands greatly increase the operative difficulties. This is due to three factors: First, the fibrous tissue of the adhesions and the lung itself may be indistinctly blended, making differentiations between the two structures almost impossible. Second, the parenchymal tissue may extend into the adhesion and contain the prolongation of a cavity, and large blood vessels may be unrecognizably imbedded within the adhesion. Third, these larger adhesions, especially those situated apically, may be of such a structure and location that it is impossible to view their entire circumference during the thoracoscopic survey. Such difficulties demand strict individualization of cases, accurate orientation and interpretation of the thoracoscopic findings. It is necessary, at this stage in the operation, for the surgeon to determine what procedure he will follow; whether complete cauterization, partial cauterization, coagulation of the parietal pleura attachment alone; or whether he will recommend some other operative procedure. The following facts are important in arriving at this decision. First, the patient may have declined the recommendations for other collapse therapy, especially thoracoplasty, or the patient's general clinical condition may have precluded this operative measure. Second, experience has taught us that, in general, certain more or less arbitrary rules are applicable in operating upon these difficult adhesions. If the adhesion is situated laterally and is of a large band or shelf structure with one or more inches between the parietal pleura and lung,

cauterization is indicated. Partial cauterization is preferable if the structure is dense and considerable time would be required for complete severance, in which instances, from one-fourth to one-half of the parietal pleura attachment can be cauterized with safety. If the adhesion is apical and presents an inch or more of free surface, partial cauterization is again the procedure of choice. If there is less than one inch of free adhesion surface, cauterization is contraindicated. Two courses are then available: first, the surrounding parietal pleura attachment may be coagulated and a higher positive pressure pneumothorax utilized to stretch the adhesion so as to permit cauterization later, or second, thoracoplasty is recommended. Thus, it is evident that with larger and more difficult adhesions, thoracoscopic examination must make the differential determination between the operative procedures of intrapleural pneumolysis and thoracoplastic surgery.

Complications

The complications incident to this operation may be divided into the immediate and the postoperative. The immediate include those which occur at the operation, such as hemorrhage and pulmonary damage. Of the 1850 collected cases, hemorrhage occurred in 1.5 per cent and was fatal in only one instance. Thus, this complication cannot be considered frequent or serious. Damage to the lung parenchyma results from technical errors and is generally due to the cauterizing of lung tissue contained in the adhesion. The partial severance of large adhesions may be followed by an immediate or delayed superimposed spontaneous pneumothorax because of a spontaneous rupture of the unsevered portion of the adhesion.

The second group of complications is postoperative and includes subcutaneous emphysema which is rarely of clinical significance. Pleural effusion occurs in practically all cases but is generally rapidly absorbed while fluid present before operation often disappears following the cutting of adhesions. The effusion may at times develop into a tuberculous empyema especially if the surfaces of the pleurae are studded with tubercles which become activated by intrapleural instrumentation. Mixed infection empyema develops by the complication of a superimposed spontaneous pneumothorax and its concurrent pleuro-pulmonary fistula. This occurs in two ways: first, as the result of the rupture of a partially severed adhesion at its pulmonary attachment and, second, as a delayed complication resulting from sloughing of the devitalized pulmonary end of the adhesion. The general clinical condition of the patient, the status of the contralateral lung, the size and type of lung perforation and treatment instituted largely determine the end result in these cases.

Our experience has been that the tissue necrosis at the site of the cauterized lung attachment or the tearing of partially severed adhesions is the most frequent cause of superimposed spontaneous pneumothorax followed by development of a pyogenic empyema. Activation of tubercles within the cauterized adhesions, the breaking down of subpleural caseating

areas, or the sloughing of the cauterized tissue is often the cause of this complication and unfortunately is unavoidable.

It has been our bitter experience to witness all the usual complications and in two instances unusual complications; in one, an extensive aspiration tuberculous pneumonia in the contralateral lung, and in another, severe postoperative hiccoughs. However, the complications usually attributed to this operation do, as is well known, occasionally develop in cases in need of but not subjected to the operation. Pleural effusion is more frequent in this group of pneumothorax cases while tuberculous empyema may develop, and superimposed spontaneous pneumothorax is likewise more apt to occur in pneumothorax cases having pleural adhesions holding cavities patent. In the 1850 collected cases operated upon, serous effusion developed in 30 per cent, tuberculous empyema in 2.2 per cent and pyogenic empyema in 1.8 per cent.[1] These figures compare favorably with those of any large group of pneumothoraces. In this small series of 17 cases operated upon by the improved electrosurgical method, three or 18 per cent developed fluid after operation, and in a like percentage fluid present before operation decreased or disappeared afterward. Tuberculous empyema developed in one case (6 per cent) and pyogenic empyema in one case. In both of these cases, the patients were less than 21 years of age, very toxic and had extensive bilateral disease with cavitation. Superimposed spontaneous pneumothorax occurred in two (12 per cent) of the cases. In one instance a purulent exudate developed and in the other only a small collection of serous fluid appeared three months later. An obliterative pleuritis occurred in one case with the subsequent loss of the pneumothorax space. Hemorrhage did not occur in this series. The worst complication is the development of a purulent exudate and although it markedly reverses the prognosis, it generally yields to correct therapy. We believe the correct therapy, at present, to be disinfection oleothorax using gomenolized oil for tuberculous empyema, and aqueous gentian violet solution for mixed infection empyema. Energetic treatment by frequent aspiration of the purulent exudate followed by irrigation and instillation of the solution indicated into the pneumothorax space yields satisfactory results, thoracoplastic surgery being used at a later date if necessary to obliterate the space. Only one of this group has required thoracoplasty.

Results

The results achieved by this operation can be adjudged only upon whether or not a satisfactory pneumothorax is produced. The late results, namely, cavity closure, are more correctly the achievements of pneumothorax therapy and although that is the end desired in all cases it alone cannot be considered as an accomplishment or a failure of the Jacobaeus operation. In this series 82 per cent of the patients had a satisfactory pneumothorax following operation. In eight cases the pneumothorax was considered excellent. In five cases the adhesions were only partially severed or others

remained which prevented the production of a complete collapse; however, satisfactory compression of the diseased area was obtained. In the follow-up study, 76 per cent had closed their cavities within or less than one year. Two of the patients died in less than six months from progression of the disease; in one, operation hastened death, but in the other life was prolonged. In one case the cavity remained patent after one year and thoracoplasty was done. A satisfactory pneumothorax was present in another patient who left our care five months after operation and his condition is unknown.

In conclusion, we wish to draw attention to this valuable adjunct in the treatment of unsatisfactory pneumothoraces due to pleural adhesions. At the same time it is desired to caution against its indiscriminate use and urge that the proper equipment be available and that experienced operators perform the operation. It is doubtless the most difficult operative procedure now utilized in the compression therapy treatment of pulmonary tuberculosis. Its complications may be serious but its many gratifying results generously repay for the diligence required in its proper execution.

REFERENCES

1. Moore, J. A.: Intrapleural pneumolysis, Jr. Thorac. Surg., 1934, iii, 276–300.
2. Matson, R. C.: The electrosurgical method of closed intrapleural pneumolysis in artificial pneumothorax, Arch. Surg., 1929, xix, 1175–1192.

THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM"; A REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS *

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IN THREE PARTS

PART I

CONTENTS: PART I

Rheumatism, using the term in its broadest sense, has just been designated "Public Enemy Number Ten" by the United States Department of Public Health. Over the world similar departments are placing this disease-group high on the list of those which present a major challenge to the medical profession and public. Chronic arthritis, the most common form of "rheumatism," is the greatest single cause of disability in temperate climates, and it produces more pensionable invalidism than any other condition except cardiovascular disease in old age. In spite of the fact that chronic arthritis is the oldest recorded disease, the medical profession has to a considerable degree ignored it. Because of this indifference, there has long existed an attitude of pessimism concerning it.

In 1924, the continuation of such a state of affairs was challenged by the formation of the "Ligue Internationale Contre le Rheumatisme." Since

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then many national committees have been created to act in affiliation with this league, the American Committee for the Control of Rheumatism being established in 1928 (Pemberton [1]). Much investigative work has been carried on; societies have arranged and journals have published symposia on various phases of the "rheumatic diseases." The profession has at last become exceedingly articulate in regard to the subject.

Interest has become so widespread, and clinical contributions and experimental investigations of merit have become so numerous, that a number of special journals have been created in other countries to present these developments.[2, 3] The transactions of several conferences and congresses have been published separately,[4] and yearly reviews of literature on these topics are now published from several countries, especially from France and Germany.[5, 6, 7, 8] In spite of the fact that workers in the United States, Canada, and Great Britain have been as active as, and indeed in some phases more active than those in other countries segregation of their publications in a special journal has not seemed wise. No systematic review of the work published in English has appeared, nor has it been comprehensively presented in foreign surveys. Therefore, at the request of the American Committee for the Control of Rheumatism, the authors have attempted to prepare a correlated synopsis of the recent significant literature of these countries. It is planned to present subsequent reviews, perhaps annually, including such editorial comment as may seem helpful. In this first review certain "background" notes are included, and critical annotations are brief.

Rheumatism as a Public Health Problem

General Incidence and Economic Considerations. Disease becomes a social problem when the person afflicted is either a danger or a burden to his fellow citizens. Disease becomes an industrial problem when it leads to disorganization of industry by causing frequent or prolonged absence of employees from their work. Thus defined, rheumatism is a social and an industrial problem of the greatest magnitude (Fox [9]). Chronic rheumatism is not the cause of much mortality, aside from the consequences of rheumatic fever. However, on account of its morbidity rather than its mortality it is productive of an enormous economic loss, the degree of which has until recently not been fully appreciated.

Statistics on the incidence of rheumatic disease have been meager. Stimulated perhaps by the investigations of the British Ministry of Health (Glover and Newman,[10] 1924) fragmentary statistics are now being made available from various quarters, but statistics in this country do not approach the comprehensiveness of those of the British. Since the report of the Ministry of Health is basic and quoted widely (Connan,[11] Fox,[12] Boyd,[13] Buckley,[14] Copeman [15, 16]), its figures bear repetition here. Records concerned the illnesses for one year of 91,000 insured persons (58,000 males, 33,000 females). During the year about 2.8 per cent (27.6 per 1,000)

of these insured persons consulted their physicians for rheumatism (total 2,510; males 1,771, females 739). Thus about 30 of each 1,000 insured men and 22 of each 1,000 insured women suffered from some kind of rheumatism during the year.

On the basis of these figures it was estimated that in England, with an insured population of 16,000,000 persons, more than 400,000 of them in any given year were suffering from one of the rheumatic diseases. How formidable is the morbidity from chronic rheumatism will be seen from the estimate that it produces one-sixth of total industrial invalidism. In 1922, rheumatism in England was responsible for a loss to workers of more than three million weeks of work and for the payment in sick benefits of about two million pounds. In 1927, sick benefits for rheumatism were about five million pounds. Adding to this the estimated loss in wages for the five and a half million weeks of work lost, the cost of rheumatic diseases to the country in that year was approximately between seventeen and twenty million pounds—$85,000,000 to $100,000,000 (Kinnear, 1928; Buckley [17]).

Dublin,[18] analyzing surveys by the United States Public Health Service and by the Metropolitan Life Insurance Company, has given us the only comprehensive American statistics on mortality and morbidity. In the United States about 10,000 deaths are charged annually to rheumatism of all forms; 4,000 deaths being directly, and 6,000 deaths indirectly, due to acute or chronic rheumatism. Of the deaths directly due to rheumatism, two-thirds are caused by rheumatic fever, one-third by "chronic rheumatism, arthritis, and gout." In recent years the death rate from rheumatism has been about 4 per 100,000 persons (between 2 and 3 per 100,000 for rheumatic fever and a little more than 1 per 100,000 for chronic rheumatism). Thus rheumatism causes an insignificant proportion of the annual death, only 0.4 per cent of all deaths.

When we turn to sickness and disability due to rheumatism, however, the picture is altogether different. The survey of the United States Public Health Service concerned Hagerstown, Maryland; that of the Metropolitan Life Insurance Company many large, widely scattered cities and towns. In all the communities surveyed, rheumatism was one of the outstanding causes of disability. The first study differs from the second in that it included all illnesses occurring over a period of time, whereas the latter was a report of sickness prevailing at a given time. The Metropolitan's figures concerning 600,000 persons showed that 164.4 persons per 100,000 were reported as suffering from rheumatism. This disease-group accounted for nearly 9 per cent of all cases of illness. As a cause of disability rheumatism was outranked only by accidents, which caused but 5 per cent more disablement; tuberculosis accounted for less than half as much, organic heart disease and cerebral hemorrhage only two-fifths and cancer less than a tenth as much. The Hagerstown survey indicated an annual rate of sickness caused by articular rheumatism and gout of 16.6 per 1,000, and in addition such illness as muscular rheumatism, lumbago, and associated conditions numbered 3.0

per 1,000. Here again rheumatism caused more illnesses than any other disease of long duration; its disability rate was therefore 16.6 per 1,000 (19.6 if one adds muscular rheumatism), that of heart disease 10.1, arteriosclerosis 1.2, cerebral hemorrhage 0.7, paralysis 1.5, cancer 1.3, and diabetes 0.9 (Dublin [18]).

A recent survey of chronic diseases in Massachusetts (Osgood,[19] Bigelow and Lombard [20]) indicated that nearly 12 per cent of the total population was suffering from some form of chronic disease. It is estimated that in Massachusetts alone about 140,000 people are suffering from chronic rheumatism (3.2 per cent of its population of 4,380,000), and that there are more cases of chronic rheumatism than of heart disease, tuberculosis, and cancer combined. There were 11,500 cases of cancer, 16,000 of active tuberculosis, 84,000 of heart disease, and 138,000 of rheumatism. In Massachusetts there are therefore over half again as many cases of " rheumatism and arthritis " as of heart disease, approximately eight times as many cases of rheumatism as of tuberculosis, and 12 times as many cases of rheumatism as of cancer. (For other recent studies on incidence see " Publication No. 2," Committee on Cost of Medical Care, Washington, 1929.)

It was estimated that in the United States, in 1932, chronic rheumatic diseases caused a loss of 7,500,000 weeks of work annually and of more than $200,000,000 to those disabled. In 1931, about 35,000 ex-service men received over $10,000,000 in disability compensation for arthritis; a number constituting 6.4 per cent of all beneficiaries of the Veterans Administration and a sum constituting 4.7 per cent of all veterans benefits (Matz [21]). These figures are increasing yearly.

Many have called attention to the relatively greater disability from rheumatism than from tuberculosis. In the past 50 years, curves of disability for tuberculosis have fallen sharply, whereas those for rheumatism have risen. Buckley [14] cites the records of a large German medical benefit association to the effect that the proportion of sufferers from rheumatic disability begins to exceed that of tuberculous children who are still of school age, but that by the age of 20 it is more than five times as great. In Germany there is three and a half times as much rheumatism as tuberculosis. Arthritis imposes upon the Swedish Pension Board an economic burden more than twice as heavy as that arising from tuberculosis. More than 12 per cent of its funds are for chronic articular rheumatism. In Sweden, 35,000 persons (0.6 per cent of the total population) are disabled by arthritis, and it is responsible for a yearly cost to the State of six million crowns (about $1,500,000, Kahlmeter [22]). As Copeman [15, 16] states, the position of tuberculosis 50 years ago was similar to that of the far more costly, but less dramatic, rheumatic disease today. Tuberculosis has been conquered largely by teamwork between far-seeing laymen and physicians who are determined to rid humanity of such domination. The same result can be achieved in the case of " rheumatism, the Captain of Crippledom."

The Clinical Content of "Rheumatism" in Its Broadest Sense

In England, "rheumatism" is a designation generally reserved by physicians for rheumatic fever. For physicians in this country and for laymen everywhere it has much broader implications. It is a term conferred by the layman on a wide variety of conditions, often bearing no other relationship than the common symptom of pain somewhere about a muscle or joint. The physician has been forced to follow suit and has come to use the convenient tag to designate any one of the commoner diseases of joints or muscles. This habit tends to foster cloudiness of thought, and a lack of appreciation of the essential discreteness of these several diseases, of their diverse etiology, and above all of the differences in treatment and prognosis.

While the chief forms of chronic rheumatic disease are atrophic arthritis, hypertrophic arthritis, and fibrositis, their symptoms are in part simulated by a number of other conditions. This discussion will therefore deal with considerably more than these three, and will include notes on progress in many allied disease-states: diseases of joints due to various types of trauma, those diseases associated with chemical or metabolic disturbances such as gout and hemophilia, those due to specific infections (gonorrheal, pneumococcic, tuberculous infections, and so forth), rheumatic fever, fibrositis, or "muscular rheumatism," bursitis and sciatica, atrophic (proliferative, infectious, rheumatoid) arthritis, hypertrophic (degenerative, senescent, osteoarthritis), and a miscellaneous group that includes psoriatic arthritis and neurogenic arthropathies. The maintenance of such a broad viewpoint will counteract one's natural tendency to limit his consideration to "inflammatory rheumatism," "muscular rheumatism," and "chronic arthritis," and to use in every case with joint pain one of these convenient labels. The breadth of the problem should not thus be delineated. Too frequently the subtle differences between a localized, chronic traumatic arthritis, of postural, occupational, or recreational origin, and "chronic osteo-arthritis" are not appreciated. In too many cases gouty arthritis is masquerading under the erroneous diagnosis of acute rheumatic fever or chronic infectious arthritis. The discerning physician will not be satisfied to establish boundaries for "rheumatism" as rheumatic fever in youth, muscular rheumatism and atrophic arthritis in middle life, and hypertrophic (senescent) arthritis in old age.

Classification of Types of Diseases of Joints and Related Structures and Their Proportionate Frequency

The following classification of diseases of joints and related structures will serve for purposes of orientation. Its inadequacies are recognized. It omits those diseases of joints which have been assigned more or less by common consent to the orthopedist (e.g. Perthe's disease, osteochondritis dessicans, etc.) or which he has perhaps quietly appropriated for lack of

interest therein by his medical colleagues. This classification, based as far as possible on known or presumptive etiology (for an etiologic classification is the eventual desire), will not satisfy those who insist on one based on demonstrable roentgenologic or microscopic evidence of pathologic change or on one adhering strictly to known facts; nor will it be entirely acceptable to those who, in the absence of full knowledge, insist on using noncommittal terms. It is a working classification, presented without defense or discussion, which seems convenient for this review (table 1).

What is the proportionate frequency of these affections? How alert must the general practitioner be to recognize some of these types; how often is he likely to encounter them? Of the many varieties and species of joint disease noted, less than a dozen will constitute the bulk of one's everyday experience with "rheumatism," even in special clinics. Nevertheless the informed physician will not permit his powers for a more discriminating differentiation to be lulled to rest. If a patient with gout, for example, is found masquerading under the banner of infectious arthritis, the rewards for keenness in diagnosis are great in terms of satisfaction both to the physician and the patient.

The relative frequency of the commoner types varies in different localities because of differences in local conditions of environment, climate, social status, or occupational hazards. Such statistics differ also depending on the type of practice concerned: home, office, or general clinic practice, general hospital practice, or the experience at spas, special clinics, or special hospitals. From his own experience (Rynearson and Hench, 1931) and that of others Hench has estimated that, in general office or general clinic practice, the relative proportions are about as follows: Of 100 people who consult their physician for "rheumatism" * (disease of joints or muscles), there will be approximately 1 case of rheumatic fever, 2 cases of gonorrheal arthritis, 3 to 5 of miscellaneous types (with ulcerative colitis, tabes, or syringomyelia, tuberculous arthritis, psoriatic arthritis, etc.), 3 to 5 of gouty arthritis, 7 to 10 of traumatic (including static) arthritis, 10 to 15 of fibrositis ("muscular rheumatism," diffuse or localized extra-articular "muscular fibrositis," or capsular fibrositis, bursitis, or sciatica), 35 to 40 of chronic atrophic arthritis, and 25 to 30 of chronic hypertrophic arthritis. (Demonstration at meeting of American Medical Association, Cleveland, 1934.)

Of 4,349 patients seen at Bath, Coates and Delicati [23] found that 52 per cent had atrophic arthritis, 16 per cent had hypertrophic arthritis, 25 per cent had fibrositis, and 7 per cent had sciatica. The incidence by sex, males to females, was as follows: atrophic arthritis 9:20, hypertrophic arthritis 9:5, fibrositis 3:2, and sciatica 7:2. In other words, for every 100 women affected by each of the following disorders, there would be 45 men with atrophic arthritis, 180 with hypertrophic arthritis, 150 with fibrositis, and 350 with sciatica.

* That is, whose symptoms are sufficient to take them to the physician. Figures on actual incidence are not available.

Fibrositis seems to be more prevalent in Buxton than at Bath. Classifying 1,496 patients with " rheumatism " at Buxton in four years, Buckley [14] noted that 13 per cent had rheumatic fever, 16 per cent had atrophic arthritis, 16 per cent hypertrophic arthritis, and 55 per cent had fibrositis (including sciatica). He explained the high incidence of the last by the fact that miners and outdoor workers constituted a high percentage of their clientele and were particularly liable to fibrositis, perhaps because the miners, for example, leave damp, fairly hot mines to enter cool air while still wearing hot sweaty clothes. In a further study, limited to men seen three years subsequently, the proportions were found to be about the same: 17 per cent had rheumatic fever, 15 per cent had atrophic arthritis, 15 per cent had hypertrophic arthritis, and 53 per cent had fibrositis. Buckley's figures approximate those of Holt [24] at Buxton Mineral Water Hospital, for 1928–1931. Only men were grouped, and rheumatic fever was not included. The proportions in 5,687 cases were: fibrositis 62 per cent, atrophic arthritis 23 per cent, hypertrophic arthritis 15 per cent.

Finally, regarding insured persons, the figures of the Ministry of Health are recalled.[10] Among every thousand insured men of all ages there were approximately four cases of rheumatic fever (i.e. one of " acute rheumatic fever," three of " subacute rheumatism "); six cases of muscular rheumatism, ten of lumbago, and three of sciatica (i.e. 19 of fibrositis); one of atrophic arthritis, three of hypertrophic arthritis, three of gout, and one unclassified, a total of 30 affected in each thousand. Among every thousand insured women there were five cases of rheumatic fever (i.e. two of " acute rheumatic fever," and three of " subacute rheumatism "); seven of muscular rheumatism, three of lumbago, and one of sciatic or of brachial neuritis (i.e. eleven of fibrositis); three of atrophic and two of hypertrophic arthritis, gout being practically nonexistent, or a total of about 21 women affected in each thousand.

Each of these and other figures must be considered from the standpoint of the type of practice concerned, as hospital records cannot be compared with those of an insured population, and the latter cannot be compared with those of the general population.

Industrial Aspects of Rheumatism

Relation of Rheumatism to Worker's Occupation, Age, and Social Conditions. Occupation may have a direct (causal or primary) or indirect (predisposing, precipitating, i.e. secondary) relationship to the appearance of rheumatism. A true occupational rheumatism is one that occurs either exclusively or principally in the given occupation. Even when trauma or some other insulting characteristic of an occupation (exposure to dampness or to thermal extremes) precipitates or aggravates a preëxisting rheumatic disease, the resulting rheumatism is not an occupational rheumatism of the direct or primary type. Most so-called " occupational rheumatism " is

TABLE I

Tentative Classification of Diseases of Joints and Related Structures

Main cause or characteristic		Types
I. Trauma:		
(*a*) Extrinsic (exogenous); generally acute and accidental. (Occupational, recreational)	Intra-articular:	
	1. Traumatic arthritis	Acute—generally due to single extrinsic trauma, e.g. "baseball finger"
	2. Traumatic synovitis	Chronic—generally due to repeated minor traumas ("micro-trauma"), e.g. from obesity, flat feet, scoliosis
(*b*) Intrinsic (endogenous); generally chronic (postural, "static")	Extra-articular:	
	1. Traumatic fibrositis ("myositis")	Acute
	2. Traumatic bursitis, tendinitis, etc. e.g. "housemaid's knee"	Chronic
II. Specific infections (known etiology): generally acute, may be chronic	Intra-articular:	
	1. Specific infectious arthritis	(1) Gonorrheal (2) Tuberculous (3) "Septic joints": staphylococcal, pyogenic streptococci (4) Pneumococcal (5) Typhoidal (6) Syphilitic (spirochetal, not arthropathy) (7) Miscellaneous and exotic; with Malta fever, dengue, dysentery, leprosy, yaws, malaria; with infection by *B. coli*, *B. diphtheriae*, *B. influenzae*, meningococci
	2. Specific infectious synovitis	
	Extra-articular:	
	1. Specific infectious fibrositis, e.g. trichiniasis; psoas abscess	
	2. Specific infectious bursitis, e.g. syphilitic bursitis	
III. "Nonspecific" infections (of unknown etiology): possibly (or probably) related to infection, focal "streptococcal (?)" or their toxins (?)	Intra-articular: 1. With rheumatic fever—(diffuse, articular, and extra-articular) 2. With "specific ulcerative colitis" 3. With scarlet fever 4. With certain skin diseases: psoriasis, erythema nodosum, scleroderma, lupus erythematosis, peliosis rheumatica 5. Atrophic arthritis: including atrophic spondylitis Synonyms: rheumatoid, proliferative, "nonspecific infectious," "infective," spondylitis ankylopoietica, etc. Extra-articular: (May occur alone or with above) 1. "Infectious (?) fibrositis": *a*. Capsular: "periarthritis"; "periarticular fibrositis" *b*. Muscular: localized (e.g. lumbago, torticollis) or diffuse "muscular rheumatism" *c*. Bursal: e.g. subacromial bursitis *d*. Perineural: e.g. sciatica of certain types *e*. Tendovaginitis: e.g. Dupuytren's ganglion 2. Rare forms of myositis (ossificans, fibrosa, etc.)	

TABLE I—*Continued*

2. Rare forms of myositis (ossificans, fibrosa, etc.)

TABLE I—*Continued*

IV. Degenerative changes in tissue	Intra-articular: 1. Hypertrophic arthritis, including hypertrophic spondylitis: Synonyms: degenerative, senescent, osteo-arthritis; spondylitis osteo-arthritica *a.* Fingers: Heberden's nodes *b.* Knees: with "static arthritis of obesity" *c.* Spine: "hypertrophic spine of elderly" *d.* Hips: morbus coxae senilis *e.* Shoulder: usually a bursitis or periarthritis rather than arthritis 2. Arthropathies: *a.* "Charcot joint"—secondary to lesions of central nervous system Tabes dorsalis, syringomyelia *b.* Pulmonary osteo-arthropathy—secondary to lesion of lung Extra-articular: Fibrositis (muscle pains and stiffness) Bursitis (subdeltoid), often associated with "hypertrophic arthritis"
V. Chemical, metabolic or "endocrine disturbance. (Some would also place either atrophic or hypertrophic arthritis, or both here)	Intra-articular: Probably chemical: 1. Gouty arthritis 2. Hemophilic arthritis 3. Arthritis of serum sickness (true allergic arthritis) 4. With ochronosis 5. Joint changes (minor) with acromegaly } Diseases essentially 6. Joint changes (minor) with parathyroidism } osseous, not articular Possibly chemical: 1. Intermittent hydro-arthrosis Entities not fully established: 2. "Allergic arthritis" from food 3. "Climacteric arthritis"—"arthritis of the menopause" 4. "Endocrine arthritis"—various types: ovaripriva A. Thyreopriva, "villous synovitis," and so forth Extra-articular: Some would add various myalgias: with lead, thyroid, excess alkalies, bismuth, arsenic, and so forth
VI. Neoplastic	Articular: 1. Primary, generally benign: e.g. chondromatosis 2. Secondary: malignant, metastatic
VII. Miscellaneous	Articular and extra-articular: 1. "Mixed types" of arthritis 2. Unclassifiable types 3. Functional types, e.g. "hysterical joints"; myalgia of fatigue and exhaustion

of the indirect or secondary type, the occupational hazards merely providing contributory factors, nonetheless important. Danischevsky [25] has estimated that, in any one year, 4 per cent of all Russian workers become temporarily incapacitated from rheumatism, with an average yearly loss of 48 days' work.

The factor of the worker's age increases the liability tremendously, as Thomson [26] and Fischer [27] emphasize. Seventy-five per cent of industrial workers over 40 suffer from some type of rheumatism. Thomson, in a survey of 500 cases of industrial accidents, found that arthritis was present in 95 cases, or 19 per cent. In 49 per cent of these cases arthritis had its onset with, or was aggravated by an injury, either occupational or causal. One-half became compensation cases. Persons more than 30 years of age who are employed in farm trade or at labor are particularly susceptible to the development of arthritis following injury. This susceptibility increases with age. Though an injury is often blamed for arthritis, Thomson was of the opinion that it may often be only an incidental factor, as other inciting and predisposing factors are also operative. However, the compensation act of Nebraska (and of certain other states) has been so interpreted as to include arthritis in benefits when proof is offered that the arthritis was the result, or a complication, of trauma, or has even been aggravated by trauma. Thomson concluded that a man over 40 years of age is a considerable liability both to his employer and to his insurance company, and that the older he gets the greater risk he becomes. This presents a problem for medical economics.

New surveys on industrial rheumatism are available (Buckley,[14, 28] Kahlmeter,[29] Fischer,[30] Coates and Delicati,[23] and Fox [9, 12]). Outdoor occupations were associated with considerably more industrial rheumatism than indoor occupations. Tempelaar and Van Breemen (1931), found that of 3,000 patients, those with outdoor employment had three to five times as much rheumatism of various types as indoor workers. Of 1,931 men seen at Bath who were affected with various types of rheumatism, two-thirds were engaged in open air occupations. The occupations in which rheumatism is especially prevalent are those entailing exposure to excess heat (metal workers, bakers), to dampness (dyeing and textile workers, miners, refrigerator workers, bath attendants, and window and bottle washers), and to extremes of weather (carpenters, farmers, laborers, postmen, locomotive engineers, policemen, chauffeurs, conductors, forestry workers, and ship builders). As previously noted, miners seem particularly liable to fibrositis: 71 per cent of 452 miners were treated for this complaint at Buxton, as compared to 45 per cent of 1,044 persons of other occupations (Buckley [14]).

Atrophic arthritis is not associated with occupational strain nearly as often as hypertrophic ("osteo-") arthritis. Among 1,114 workers Fischer [30] found that only 1 per cent had atrophic arthritis, whereas 48 per

cent showed "degenerative joint changes." Although his data convinced him that the "deforming arthropathies" originate most frequently from static, functional, and traumatic causes, Fischer does not believe that occupational injuries alone very often produce the arthropathy but that a constitutional disposition is the deciding factor. Freund [31] is of the same opinion.

In Sweden there is more invalidism from "chronic articular rheumatism" in the country, than in towns and cities. The lowest incidence was in large cities. The greatest invalidism is among landworkers and peasants.[29] In Russia also, villagers are said to be thus affected twice as often as those in cities (Danischevsky [25]). In Germany, arthritic invalidism is at a minimum where working and housing conditions are good (Edstrom [32]).

The general conclusion of a discussion, led by Warner,[33] on the relation of soil and climate to rheumatic diseases was that climate is not the prime cause of rheumatism, but that climate has an effect on people subject to rheumatism.

Diseases of Joints Related to Trauma

Traumatic Arthritis: General Considerations. While fibrositis and atrophic arthritis can be produced indirectly (precipitated or aggravated) by occupational trauma, Fischer [27] was of the opinion that hypertrophic arthritis is the only form of arthritis for which mechanical trauma is solely or mainly responsible, and that this true occupational arthritis generally only involves shoulders, hands, and especially elbows. The "deforming arthropathies" of the hip, knee, and feet, he believes, are caused more by static influences than by occupation.

The results of trauma to articular and periarticular structures depend largely on the type, severity, and duration of the injury. Due to variations in resistance (the factor of constitutional predisposition), joints may react differently to identical trauma. In one case a temporary, perhaps minor, disability and rapid healing results; in another case chronic arthritis may eventuate. The varieties of injury which affect joints are in general due to (1) accidental, (2) recreational, (3) occupational, and (4) postural trauma. Accidents, such as blows and falls, provide an acute exogenous (extrinsic) trauma. Recreational and occupational hazards may result in either an acute (gross) or chronic (micro) trauma. Postural or static defects provide the basis for an endogenous (intrinsic) chronic trauma.

There is no difficulty in recognizing an acute traumatic arthritis or periarthritis, but when the onset of joint disability is insidious and its course chronic, its connection with repeated minor injury may be forgotten or may seem too remote for consideration. The rôle of trauma may then be missed entirely. It is difficult to determine the interval within which an arthritis may be considered the result of a single injury. In half of 48 cases studied by Thiem [34] the joint trouble began within eight days, but in others the interval was four weeks and in two cases it was three months and six months

respectively. As to the results of repeated minor trauma, the earliest occurrence of a deforming arthropathy after starting the responsible occupation was three years, and the latest was 30 years (Fischer [30]). Various types of work induced the same type of deformity, and no particular relation existed between the severity of the resultant joint injury and the length of time in which any particular work was pursued. Hence the factor of individual susceptibility or constitutional predisposition seemed crucial. Fox [9,12] repeats the warning of Weisz [35] that a single strain or contusion may be followed by years of pain and limitation of motion even with no obvious anatomic change. Atrophy of muscles may ensue, and the whole body may be affected by a traumatic neurosis. Hence all employers should have treatment instituted promptly, early use of heat and movement, with adequate physical and roentgenographic examination to lessen the demand for compensation benefits and the chances of neuroses.

To study the response of articular structures to injuries of various sorts, Key [36] resected a rectangular portion from the patellar aspect of the femur; hypertrophic arthritis resulted. A similar type of arthritis was produced by various chemical insults to cartilage. Articular cartilage is the most vulnerable tissue of a joint, and if it is injured in any way and the joint continues to function, the result is hypertrophic arthritis regardless of the type of injury.

Others also have produced hypertrophic arthritis in animals by various kinds of injury to joints. The results are difficult to interpret, according to Doub,[37] who favors reliance on clinical opinion that tends to show that a severe single, or a mild but repeated type of injury can and does produce the picture of hypertrophic arthritis. According to Doub opinions are divided as to whether injury can aggravate an already existing arthritis. (To us it seems well established that it may.—Ed.) To establish the diagnosis of a true traumatic arthritis Doub insisted that there must be proof of an injury and exact information regarding its severity, the injury must have been applied to the joint in question, information must be obtained as to the previous function of the joint in question, the time interval between the injury and the occurrence of pathologic changes must be within the generally accepted limits (a few months to a year); and there must be clinical and roentgenologic evidence of pathologic changes in tissue. The roentgenologist, however, can only report the presence or absence of pathologic deviations present in the films and clinical signs are more important. Roentgenologic evidence alone can not decide the question. If in cases of preexisting arthritis it is decided that a traumatic arthritis also exists, compensation should be paid only until the previous state of use of the joint has been restored. Unfortunately, as Cotton [38] points out, the determination of the previous state of the joint may be difficult to make, since as a rule there has been no clinical or roentgenologic examination made before injury.

Effect of Fracture on Articular Cartilage. The mechanism whereby joint cartilage is repaired following injury or disease is not fully understood.

Repair differs where perichondrium is present. The central part of articular cartilage has no perichondrial covering. Reparative processes in this area are said to be characterized by the fact that no new formation of cartilage from proliferating cartilage cells occurs, and defects of cartilage may or may not undergo cartilaginous repair. Where, however, the defect involves the underlying cancellous spaces, a sluggish formation of new cartilage is seen, resulting from metaplasia of the connective tissue cells of the exposed cancellous areas.

Under certain conditions, such as that seen in articular cartilage of the hip joint following complete intracapsular fracture of the neck of the femur, Santos [39] has demonstrated that, if the blood supply remains intact, articular cartilage may first undergo degeneration, then resorption, as the result of invasion of cartilage from subjacent bone marrow, and thirdly, regeneration from active formation of new hyaline cartilage, in part from overlying vascular pannus of fibrous tissue but to a greater extent from a proliferation of surviving cartilage cells. The invasion of cartilage from subjacent bone marrow is like that seen in some cases of arthritis deformans. Where the trauma caused an interruption in vascular supply, such processes of cartilage repair do not occur. The femoral head becomes necrotic, and invasion of articular cartilage from subchondral marrow and proliferation of cartilage cells does not result.

Traumatic Rheumatism; Specific Types. Some of the common designations for traumatic disease resulting from occupational and recreational injury to joints are the "glass arm" of musicians and ball players, "golfer's arm," "motorist's arm," "soldier's shoulder," "tennis elbow," "miner's elbow," "tennis-player's wrist," "baseball fingers," "engineer's spine," "farmer's back," "tennis back," "driver's thigh," "cyclist's thigh," "weaver's bottom," "nun's or housemaid's knee," "rider's knee," "game knee," "tennis leg," "fencer's bone," "dancer's bone," "nurse's feet," and "policemen's heel." Similarly, various muscular affections are recognized and designated as "writer's, waiter's, auctioneer's cramp" and so on.

A pathologic basis for some of these conditions has not been exactly defined. In some instances they represent not one entity but one of several affections. The underlying condition in "glass arm" is usually thought of as a subdeltoid or subacromial bursitis (with or without involvement of the capsule of the shoulder joint or calcification of the supraspinatus tendon). Others, however, define it as a "neurosis marked by spasm of the pronator teres muscle." "Driver's thigh" is generally considered to be a postural sciatica; "weaver's bottom," a bursitis at the ischial tuberosity; "housemaid's knee," a prepatellar bursitis; "tennis player's wrist," a tendovaginitis. Affections of the shoulder are common in several occupations: in stokers from shovelling, gardeners from digging, miners from hewing, chauffeurs who use a hand brake, plasterers who must wield trowels at the height of their heads, and workers with compressed air tools (Ray,[40]

Fischer,[30] Freund [31]). The constantly repeated vibrations of the pneumatic drill may produce eventual splitting and destruction of articular cartilage.

" Tennis Elbow," Epicondylitis Humeri, Radiohumeral Bursitis. Tennis elbow, according to Carp,[41] may represent either an inflammatory involvement of the conjoined tendon (of the extensors) at the lateral epicondyle of the humerus, or of a structure in close proximity thereto, such as the radiohumeral bursa. The term is a misnomer, as the condition it represents may occur not only as a result of sports requiring the use of a tennis or squash racket, but of others such as golf, polo, and baseball, and also of occupations demanding lifting and sudden flexion and extension of the elbow, such as are required of clothes pressers, violinists, blacksmiths, telephone operators, salesmen carrying grips, and housewives. Its cause may be chronic trauma or acute injury over the lateral aspect of the elbow. It is frequently diagnosed as a " sprain " or as " rheumatism." Its symptoms may appear acutely, or be chronic and mild. There are pain, tenderness, and sometimes swelling and heat in the region of the epicondyle. The pain may be of a sudden, sharp, darting character, causing a quick cessation of the movement producing it, or it may be dull and constant, radiating to the arm, forearm, or hand. Extension of the elbow, pronation, supination, or tight flexion of fingers may increase the pain. Extension of the wrist may relieve it. Weakness of extensor muscles of the forearm is usually present, with a weak hand-grip. (According to Hansson, 1930, passive motion of the elbow, forearm, and hand may be quite painless and free, as is active motion of the flexors when the forearm is supinated.—Ed.).

Since Bernhardt's first description of it (1896) as a neuralgia, others have considered tennis elbow to be due to periostitis of the epicondyle, a myofascitis of the extensor muscle at the external condyle, a radiohumeral bursitis, an arthritis of the radiohumeral joint, a tear in the extensor carpi radialis longus, an affection of the supinator brevis muscle, an involvement of the capsule of the elbow joint or of the subcutaneous fat, fascia, and periosteum of the epicondyle, a malalignment of the radial head and of the lower end of the humerus, or " adhesions." Osgood described it as a radiohumeral bursitis (Osgood-Allison, 1931). In Carp's study of eight cases roentgenograms showed a cloudy, distended, frequently calcified, radiohumeral bursa and at times an osteitis of the epicondyle. The treatment of choice was to rupture the bursa by firm digital pressure, applied over the epicondyle and radiohumeral joint. Prompt, often dramatic, relief may be expected. Resorption of calcium follows. In some instances conservative treatment consisted of heat and rest. The forms of treatment advocated by others (manipulations, splints, roentgen therapy, infiltration with procaine) are considered less useful. Excision of the bursa is not recommended unless manipulative rupture, or rest and heat, fail to give relief. One calcified bursa was removed and the pathologic changes were described.

" Chauffeur's Shoulder." In connection with London busses, rheumatic affections seem to be the special hazard for both man and beast. We have

been told of the localized exostoses and injured cartilages seen in London cab horses (Burt, 1928). Nairn [42] has now described an osteo-arthritis of the shoulder joint of London busmen, the etiology of which he believes to be trauma from gear shifting and not from exposure to inclement weather as one might at first assume. In busses, gears are generally stiff; to change them requires considerable effort and jarring. Among busmen driving the older buses, with right hand gear-shifts, the arthritis affected the right shoulder joint; for those driving new busses, with left hand gear-shifts, the left shoulder was involved. Diathermy and massage gave relief.

"Driver's Thigh." A neuralgia of the sciatic nerve may occur among those who drive motor cars continually. The symptoms, according to Hoets,[43] may vary from an ill defined feeling of fatigue of the thigh muscles, to those of classic sciatica. The cause of the sciatica is the continued use of the accelerator pedal, the leg being held in one position for long periods. Hoets has given diagrammatic evidence of the relation of faulty seats to this condition. If the driver sits badly, or if the rear springs of the seat have given away, an abnormal tilt may engender unusual pressure and eventual injury to the sciatic nerve just before its division in the lower third of the thigh. Treatment consists of the proper adjustment of the faulty seat.

Titus [44] stated that serous effusions are dissipated from joint cavities not by blood channels but by means of lymphatics. Therefore, in cases of traumatic synovitis one must not expect great results from diathermy, although some relief of pain may be afforded. Some forceful mechanical influence, such as massage above the knee and up the thigh, is required to encourage the forcing of the effusion into the lymphatics. (Considerable experimental evidence exists, however, that effusions are in part dissipated via blood vessels.—Ed.) Heat is indicated preliminary to massage. Diathermy will not heat the inside of the knee, and a heat lamp will suffice. Titus favors the use of static currents, and claims that fluid can generally be removed in three or four treatments by "the obvious decongesting action" of high-voltage currents provided by the static brush discharge. An ace bandage in a "figure of eight application" is used in the interval between treatments.

Hemarthrosis. Simple traumatic hemarthrosis at times necessitates aspiration to remove blood and fluid in order to prevent formation of disabling adhesions which Key and others have shown may result from experimental as well as clinical hemarthrosis. Even so, repeated aspirations may be necessary and convalescence prolonged. The injection of air into joints after aspiration has, according to Johnson,[45] hastened recovery and given prompt relief of pain. Thirty-two cases so treated escaped complications or permanent disability.

Traumatic Bursitis and Ganglion Formation. Three patients with acute exacerbations of chronic prepatellar bursitis, presumably due to trauma, were treated by Diamond [46] by aspiration of bursae and injection of 5 c.c. of tincture of metaphen, 1:200. Rapid reduction of swelling and apparently com-

plete occlusion of the bursal sac occurred, with no recurrence after 11 to 20 months. One must be sure that the bursa does not communicate with the knee joint, as such fluid would cause injury thereto. When adhesions in bursae have caused sacculation, an injection of each sac is necessary.

A very large bursa, placed over the ischial tuberosities and analogous to " weaver's bottom," was removed by Fraser [47] on the assumption that it was a lipoma. It weighed 2 pounds 10 ounces; its circumference was 18½ inches, and its diameter 6½ by 6 inches.

A ganglion is a cystic swelling which contains thick mucoid matter. It usually has a thin wall and occurs in the region of the capsules of joints or tendon sheaths. The cause of such ganglions is unknown, although trauma seems to be an important agent. They occur more often among women than men, and more often in the hands and feet, especially in relation to the capsule of the wrist. E. S. J. King [48] has described the three stages of their development: (1) marked proliferation of spheroidal cells, with mucoid material in and between the cells, (2) similar cells in the wall of a cavity containing mucoid material, and (3) a well-defined cavity and a well-formed wall containing spindle cells.

Industrial Backache. The correct diagnosis and disability-assessment of the " industrial back " is an almost daily requirement of the " company physician " and the orthopedist. Such backaches provide a problem of great economic importance. Confusion concerning their differentiation results from lack of complete understanding of the anatomy and pathologic physiology of the spine, and from the misconception that the spine is an especially strong structure, immune to most of the conditions that beset other joints. Until recently the weaknesses inherent in the back, so obviously revealed since man began the experiment of walking on two instead of four legs, have not been fully appreciated. The spine is a flexible structure basically similar to an arm or a leg, with its units, the vertebrae, made up of the same structures as a knee or ankle. Kidner [49] emphasized the fact that joints of the spine are subject to the same ills as other joints; traumatic or infectious synovitis, or that secondary to fracture, sprains, overstretching or rupture of ligaments; effusions and adhesions, strains, overstretching of contiguous muscles, infectious or traumatic arthritis, and minor as well as major fractures. Affections of muscles are probably the most common cause of backache. They become flabby, relax, and lead to unstable articular apposition, bad posture, and chronic strain. They are subject to strain, fatigue, rupture, or inflammation. Intervertebral disks are susceptible to injury or to disease. The nerves, as they leave the spine, are extremely liable to irritation or pressure.

Kidner has reviewed the common types of industrial backache, and summarized the symptoms and signs whereby injuries to the back can be recognized. The following are the more frequent types of disturbance: 1. Injury to the fibers of the erector spinae muscles, such as may occur when a man carries a heavy weight, and which is characterized by sudden pain

that then lessens only to increase and keep its victim bedfast the next day. 2. Strain at the lumbosacral or sacroiliac joint; sprain of these joints, so liable to injury, should be considered as presenting the same problem as sprain of an ankle, i.e., tearing of ligaments, hemorrhage in periarticular tissues, possibly effusion into the joint, pressure on nerve roots, and consequent pain. 3. Crushed or impacted fracture of a vertebral body may occur after only slight trauma; it is commonest at the dorsolumbar junction and is frequently overlooked when a lateral roentgenogram is omitted. 4. Injuries of the intervertebral disks are less frequent causes of backache. Roentgenograms may show a bulging hernia of the nucleus pulposus through the annulae fibrosus. Laminectomy for the relief of pressure may be necessary if the hernia enters the vertebral canal and produces pressure on the cord. If it pushes through the bony plate of the adjacent vertebral body in the spongy bone, the moderate pain may be relieved by rest and a back brace. 5. Spondylolisthesis is probably due to a congenital failure of union between the normal anterior and posterior centers of ossification of the arch of the vertebra. This permits the vertebral body to slip slowly forward, with stretching of the cartilaginous union under the strain of weight bearing. It is often a chance finding in otherwise normal persons. When first discovered, after a back injury, its appraisal is difficult and its presence increases difficulties in treatment.

While acute backaches incident to industrial trauma generally disappear with reasonable treatment, neglected cases become great problems. Persons afflicted present the syndrome of pain, which prevents working, stooping, lifting, and sometimes standing or walking. The syndrome results from real pathologic changes, habit pain, the sympathy of relatives, or the chance of disability compensation. Malingering and overstatement must be recognized, but it is even more important to recognize the undoubted evidences of pathologic changes that may be present: real protective muscle spasm, real sensitivity to pressure over the lesion, limitation of movement but only to the degree appropriate to the suspected lesion, constancy of symptoms and signs, and above all adequate roentgenographic data and, when indicated, a neurologic examination. A prerequisite to successful treatment is the patient's desire to get well. Kidner has outlined the treatment of his choice: rest, sometimes for several weeks in bed, and at times in a cast, other orthopedic appliances, as necessary, and the appropriate types of physical therapy.

Prevention and Treatment of Industrial Rheumatism. Measures suggested for the prevention of various types of rheumatism incident to industry are summarized in a recent symposium (Fox,[9, 12] Neligan,[50] Copeman,[15, 16] Boyd [13]). Miners should wear light working clothes to permit aeration and minimize stagnant sweat. Before facing changes in temperature outside the mine, they should bathe at the mine head and change to warm, dry clothing. Workers in cold places should be provided with insulated clothes, especially boots and leather pads, warm canteens, hot food, and hot foot-baths. For those exposed to wet, waterproof clothing, warm

boots, and warm dressing rooms are essential. In all occupations in which there is excessive perspiration an abundance of bland drinks, such as oatmeal or barley, is desirable. The joints and muscles of workers, e.g., drillers who are subject to prolonged vibration or other trauma, should be protected by shock insulators, leather pads, or other devices. There should be pauses from fatiguing work. Predisposing factors of industry aside from trauma should be minimized by the avoidance of damp offices and houses, adequate sunshine, proper hours for food and rest, and reduction of avoidable mental and physical strain. Social workers can do much to investigate, correct, and control such phases of the problem.

The British insurance physician is handicapped in that although he can guarantee the victim a pension, he cannot set machinery in motion for his admission to a spa hospital or to special clinics for physical therapy. Rapid return of the patient to industry and the avoidance of progressive deformity and disability usually necessitate more special care than the physician can provide the patient who is confined to his home. While more " rheumatism units " and " special physical therapy centers " are being established, it is imperative that they be made available to the indigent worker whose dole so far covers little more than maintenance and does not provide for prolonged treatment. When treatment can be begun early, great disability can be prevented. By evening physiotherapy sessions, many can be kept at work during the day (Ray [40]). The patient's occupation may have to be changed. Fox listed as those occupations least harmful to an existing rheumatism: office work of various kinds, teaching, library or laboratory work, seamstress, telephone exchange, book binding. The tobacco business is especially favorable, as cigars must be kept in a warm dry atmosphere.

Disease of Joints Due to Infections of Known Type

Acute Pyogenic Arthritis; " Septic Joints." Although the treatment of acute suppurative arthritis (" empyema of joints," " acute epiphysitis ") is generally surgical, diagnosis and preoperative care are a medical problem. Its causes, diagnosis, and treatment have been reviewed by Caldwell,[51] Bisgard,[52] Sevier,[53] and Foster.[54] It most frequently affects the joints of children, the hip especially, less commonly the knee, ankle, sacro-iliac region, shoulder, elbow, or wrist. " Septic arthritis " arises in three ways: (1) from a hematogenous infection localizing in a synovial membrane; (2) by extension from a hematogenous type of osteomyelitis from bacterial infarction, affecting closely contiguous or intra-articular bone, and (3) infrequently, from penetrating wounds of joints.

Common types of infection responsible are otitis media, umbilical infection, scarlet fever, tonsillitis, the " ordinary sore throat " (Sevier [53]), gonococcal and pneumococcic infection, and those after circumcision. Symptoms are: sudden onset of high fever, leukocytosis, and pain and tenderness in the involved joint. When a hip is affected, a characteristic

position is assumed, due to muscle spasm, namely, flexion, with either abduction and external rotation or adduction and internal rotation. The latter favors spontaneous dislocation of the femur. Pain may be referred to the lower thigh, knee, or calf, but passive motion of the knee is painless and that of the hip is very painful.

For the first 10 or 15 days, roentgenograms are usually negative and no bony change is visible, although after five or ten some narrowing of cartilage space may be visible. When a diagnosis of pyogenic arthritis is suspected, one should not rely on a negative roentgenogram but should early perform diagnostic aspiration. Aspiration, and even exploration, will do no material harm in cases of nonseptic arthritis, but if delayed in cases of pyogenic arthritis, extensive and irreparable injury may result (Foster [54]). If pus is obtained on aspiration, immediate surgical drainage may prevent further destruction of cartilage by proteolytic enzymes from the leukocytic exudate. Muscle spasm is then relieved by fixation and traction. (Surgical drainage is not indicated in every case of septic arthritis; it depends on the degree of sepsis and the patient's reaction. Some cases, such as the gonorrheal type, may respond well to aspiration and washing, without need for more extensive drainage.—Ed.)

The course and prognosis depend on the nature and site of the articular injection. If articular sepsis arises from infection localizing in synovial membrane, the cartilage may be destroyed but adjacent bone is seldom invaded; the prognosis is then good, nearly normal function frequently being restored. If sepsis arises from infected foci in adjacent bone, however, such as from osteomyelitis of the neck of the femur, femoral epiphysis, or pelvic bone, destruction of bone occurs, the synovial membrane and cartilage are invaded secondarily, the latter being destroyed, and ankylosis or pathologic dislocation of the head of the femur is the usual sequel. (Phemister is of the opinion that epiphyseal infection is much less common than diaphyseal infection.)

At aspiration or surgical drainage one cannot always be certain from whence the infection arises. If fever subsides and prompt improvement is noted, the local origin of infection is usually in synovia. If fever fails to subside within 10 days, a source of bone infection must be suspected; roentgenographic examinations must be repeated and, if infected bone is found, drainage must be performed. Bacteriologic studies usually reveal *Staphylococcus aureus,* pneumococci, or streptococci. Such studies are helpful, as Beekman and Wilensky [55] (cited by Bisgard) reported that staphylococci usually signify infection of contiguous bones, whereas infection with pneumococci or streptococci generally results from blood-borne metastatic infection affecting synovia.

Caldwell [51] studied cases of septic arthritis in which 18 hips (of 17 children) were affected. In six hips a hematogenous infection had localized in synovia; in 12 hips intra-articular infection arose from adjacent osteomyelitis. One of the children with a septic synovitis died of septicemia. Results in

the 16 cases in which children survived (17 hips being affected) were as follows: normal or nearly normal motion was restored in eight hips, in five of which there was chiefly synovial inflammation and in three infection from osteomyelitis. Partial or complete ankylosis resulted in the nine additional cases of sepsis secondary to osteomyelitis, four with solid ankylosis and five with pathologic dislocation and limited motion. The average duration of illness before operation was 13 days, the average stay in the hospital two and a half months.

Of 217 cases of pyogenic osteomyelitis Bisgard [52] noted an associated septic arthritis in 51 cases (24 per cent) in 42 of which it arose by direct extension from an adjacent diaphyseal infection. In nine cases the joints appear to have been involved by hematogenous infections, presumably from remote foci of osteomyelitis. Only 13 per cent of joints infected by direct extension regained a good range of motion, 65 per cent became ankylosed, and the rest suffered varying degrees of functional limitation. A third of those infected from distant sources regained a good range of motion and 65 per cent developed ankylosis; the rest obtained variable limitations.

Gonorrheal Arthritis and Synovitis. Gonorrheal arthritis is the most common form of joint disease of known infectious origin. Of 13,000 patients with gonorrhea seen by Lees,[56] 388 or about 3 per cent (3.2 per cent males, 1.8 per cent females) developed gonorrheal arthritis. Contrary to experience in this country arthritis did not complicate any of the 150 cases of gonorrheal vulvovaginitis in children. McCahey,[57] who has written a short account of the literature on this disease, believes that urethral trauma, trauma to the joint, and previous rheumatic arthritis do not predispose to the development of gonorrheal arthritis.[58] According to him, infected seminal vesicles are a more common focus than prostatic infection; metastatic infection " occasionally " arises from the anterior urethra.

Lees classified acute joint involvement with gonorrhea as follows: (1) arthralgia of one or more joints, (2) acute synovitis, (3) acute arthritis, in which cartilage, synovia, capsule, and periarticular tissue are involved and a serofibrinous exudate is present, and (4) acute purulent arthritis, a rare complication which may result from gonococci alone and not necessarily from a mixed infection. Subacute and chronic cases may be of two types: (1) synovitis, (2) arthritis with involvement of cartilage, synovia, and periarticular structures.

An arthralgia may represent merely a toxic reaction. When joint exudates arise, actual articular invasion with gonococci has occurred. In 80 per cent of Lees' cases of gonorrheal arthritis joint manifestations occurred within the first four or five weeks of the primary infection. It was seen as early as the fifth day in a case of urethritis; in chronic genitourinary infections the onset of arthritis may be later. Arthritis has been recorded as having occurred 15 or 20 years after the onset of gonorrhea, generally having been induced in such cases by instrumentation or pelvic surgery.

Only 15 per cent of Lees' cases were monarticular; 85 per cent were polyarticular. The order of frequency of involvement was: knee in 64 per cent, ankle in 37 per cent, metatarsophalangeal joints in 35 per cent, shoulder in 23 per cent, wrist in 14 per cent, metacarpophalangeal joints in 14 per cent, elbow in 2 per cent, hip in 4 per cent, intervertebral joints in 3 per cent, and temporomandibular joint in 2 per cent. Sternoclavicular joint involvement was not noted, an area involved in 2 to 3 per cent of cases according to the statistics of others.

The symptoms of gonorrheal infection of joints are variable depending on the virulence of the infecting agent and the resistance of tissues. An acute arthritis of one or more joints may follow a few days of fleeting arthralgia. The temperature may be 101 to 103° F. Pain, sweating, and fluctuations in joints are more marked in those rare cases where actual suppuration occurs. Lees agreed that roentgenographic changes in gonococcal arthritis are not diagnostic. In 72 cases of gonococcal arthritis Delacroix [59] noted decalcification of bone-ends and a rarefying osteitis proceeding to destructive ankylotic changes. A severe arthritis may accompany a "mild gonorrhea."

With roentgenograms taken of air-filled joints, in two cases of acute gonococcal synovitis in which experimental pneumo-arthroses were produced, Ginsberg [60] followed the sequelae of effusions and noted characteristic adhesions in the suprapatellar pouch responsible for later mild stiffening. The effusion, which escaped absorption or aspiration, became static in different portions of the suprapateller pouch and the joint proper, and became organized.

A positive complement fixation test to gonococci is considered by Lees and by Green [61] to be of great value; it was positive in 75 to 80 per cent of Lees' cases. A negative test, however, does not exclude gonococcal causation. The sedimentation rate is rapid, as in acute rheumatic fever and atrophic arthritis. It is of little value in differentiating various forms of arthritis, but repeated tests are helpful in gauging the activity of the process during the course of the disease. (Oppel, Myers, Keefer.[62])

Treatment of Gonorrheal Arthritis. Treatment must be general, to the original focus of infection, to infected joints, and for the septicemia or pyemia. Lees [56] discussed the value of various forms of therapy: rest, diuretics, medicines, prostatic massage, urethral irrigations, foreign protein therapy, and various forms of physiotherapy. In the acute stage, heat, rest, and immobilization are indicated, but movement and massage must be instituted as soon as possible to prevent permanent loss of motion (Lees, Ginsberg). The effects of high-frequency currents (diathermy) to prostate gland and vesicles, as introduced by Cumberbatch and Robinson, have been disappointing to Lees who advocates "specific therapy" with "detoxicated vaccines." Delacroix is convinced of the value of radioactive mineral waters in restoring normal calcification to the affected bones.

Conservative (i.e., nonsurgical) measures are favored except in pyar-

throsis, in which case arthrotomy is advocated (Lees,[56] Neely[63]). The value of irrigation is noted: with bichloride solution (LeBreton[64]), with Pregl's solution (Thomson[65]), and with warm saline solution. Ginsberg felt that benefit resulted from injections of air.

The method of treatment that bids fair to supplant all others for gonorrheal infections, especially of joints, is hyperpyrexia by "superdiathermy," radiothermy, or hot air-conditioned cabinets. Since 1931 brief reports have appeared indicating that rapid sterilization of joints and the genito-urinary tract can be accomplished if by these means the patient's temperature can be elevated long enough to reach or exceed the thermal death point of various strains of Neisseria gonorrhoeae. The thermal death time of fifteen or more strains of gonococci in vitro has been determined as about 5 hours at 41° to 42° C. (Carpenter, Boak, Mucci, and Warren[66]). A few strains are more resistant and need the same temperature for longer periods or a higher temperature for shorter periods. Carpenter and Warren treated patients with gonorrheal arthritis with radiotherapy and superdiathermy. Patients were "usually cured," although in one case there was complete failure after seven hours of heat at 41.5° C. In this case the thermal death point of the gonococcus isolated from the joint was much higher than the amount of fever induced in the patient. Nine patients were treated by two fever sessions of five hours each with "very encouraging results" by Bishop, Horton and Warren.[67] Acute arthritis subsided rapidly, redness and tenderness disappeared, and mobility was gradually restored. Chronic arthritis became painless and there was gradual relief from stiffness. Tenney[68] believed that if a temperature of 106° F. is maintained for two to four hours, it acts almost as a specific against gonorrheal arthritis, as he believed the thermal death point of the organism to be about 104° F. In two cases in which the patients were treated by Warren and Wilson[69] symptoms subsided entirely after one or two sessions of fever at 41.5° C. for five hours.

A patient of Berris[70] with acute gonorrheal arthritis received no relief after four treatments each at 103° F. for four hours, but a patient with "probable gonorrheal arthritis" of six months' duration obtained "complete relief" after six treatments at 102° F. for three hours. Simpson, Kislig and Sittler[71] obtained gratifying results in the treatment of gonococcal and other types of infectious arthritis using radiothermy and later an improved hot air-conditioned cabinet. Atsatt and Patterson[72] treated eight patients with gonorrhea of the joints and genitals by general diathermy. In all eight cases the arthritis was cleared by one to five treatments, at temperatures not over 103.5° F., for periods of five hours or less, and in all but one case negative smears were found thereafter. For opinions on the virtue of different methods, varying lengths of fever sessions, prevention of reactions, and contraindications and so on, reference should be made to papers cited.

Complications and Prognosis. According to Lees,[56] the prognosis in

cases of gonorrheal arthritis in which suppurative reactions are not present is "invariably good" as far as joints are concerned, particularly if roentgenograms show no destruction of articular surfaces and if proper treatment is instituted. Myositis is the commonest complication, being present in 80 per cent of the acute and all of the less chronic cases. Keratodermia blennorrhagicum was noted occasionally.

Tuberculous Arthritis

Tuberculous arthritis is characterized by pain, swelling, and stiffness of the affected joint or joints, increased local heat, and atrophy of surrounding tissues. Redness may or may not be present; in late stages it is usually absent. The condition is indolent, is characterized by remissions and exacerbations, and is usually progressively destructive unless the disease is checked by resting the joint in splints or by arthrodesis. The onset is usually gradual. A third to a half of the patients suffering therefrom present an associated visceral tuberculous lesion. Roentgenograms are not characteristic in early cases or in cases in which there is advanced destruction. In cases in which the disease is of moderate duration, roentgenograms are usually highly suggestive, atrophy, marginal erosion of bone, and interruption of the articular cortex being noted. Marked haziness of the joint and synovial thickening may be present. The joint space is usually well preserved until the late stages of the disease, because articular cartilage is peculiarly resistant to toxins of tuberculosis. An absolute diagnosis of tuberculous arthritis rests on the isolation by aspiration or biopsy of viable bacilli of tuberculosis in synovial fluid or membrane, as shown by inoculation of guinea-pigs and the demonstration of tuberculous tissue, that is, epithelial cells and lymphocytes in characteristic configuration with or without the presence of necrosis and foreign body giant-cells.

Roentgenographic Data. A tuberculous synovitis develops whether the primary focus of tuberculosis is in bone or synovia, and granulation tissue forms which tends to invade cartilage. Phemister and Hatcher [73] correlated the pathologic and roentgenographic findings. In some joints articular cartilages fit together accurately, while in others, particularly the knees, contours are different so that there are large areas of both free and contacted surfaces. In joints with both free and opposed surfaces of cartilage, the free portions are destroyed while the contacted areas are largely spared except at the margins. Subchondral granulations, free from tubercles, develop and aid in detaching the articular cartilage, which may persist for some time due to the absence of proteolytic ferments in the exudate. At this point roentgenograms show regional atrophy of bone, reduction of density of the bony articular cortex, and preservation of the normal width of the joint space. In joints like the knee, with areas of noncontacted cartilage, the articular cortex may be destroyed by surface granulations before any changes due to subchondral granulation may be detected in the articular

cortex of the opposed portions. Eventually, narrowing of the joint space is seen, the result of complete destruction of articular cartilage. In advanced stages, bilateral opposing sequestra are formed at the traumatized points of contact and weight bearing. These are shown in roentgenograms as relatively dense, conical shadows with incomplete lines of demarcation. Bony ankylosis almost never occurs, even when these secondary sequestra are present.

In adults, primary osseous tuberculosis is usually located in the epiphysis bordering the joint, although it sometimes extends into the articulation. The changes just described cannot be recognized in roentgenograms until atrophy and sequestration (usually unilateral) have set in. In children, owing to their relatively thick articular cartilages, destruction and detachment of the noncontacted portions are less complete. In swollen joints, with thinner cartilages and in older children, the pathologic and roentgenographic picture resembles more that seen for adults. Secondary invasion of bone at weight-bearing points produces extensive bilateral necrosis without sequestration.

The clinician, suspecting a tuberculous arthritis, places considerable reliance on the diagnostic abilities of his roentgenologist. Pomeranz [74] reminds us that, contrary to opinion, an early or positive roentgenologic diagnosis is no easy task. An accurate interpretation of this disease is extremely difficult, as criteria utilized in the roentgenologic diagnosis of tuberculosis are subject to diversified exceptions. The usual roentgenologic changes are: synovitis and periarticular swelling, atrophy of bone or sclerosis, bone production and destruction in epiphysis and metaphysis, narrowing of joint space, sequestration, and the presence of cold abscesses or sinuses. In the genesis of tuberculous arthritis most or all of these changes are present. The roentgenogram is but a record of the disease at a given moment.

Synovitis, periarticular swelling, and atrophy of bone are common to all arthritides and are of limited value in the diagnosis of tuberculous arthritis. Atrophy of bone is usually marked, but its intensity is modified by numerous imponderable factors which complicate diagnosis. Sclerosis and bone production occur in tuberculosis even in the absence of a mixed infection. When sinuses exist, bone production may be absent. Diaphyseal tuberculosis in long tubular bones is rare, and roentgenologically the diagnosis is impossible. Wedge or cone shaped lesions are usually tuberculous. "Kissing" sequestra (occurring on both sides of the joints) are common in tuberculosis. Narrowing of a joint space which occurs late in an infection, despite associated destructive changes, is strong presumptive evidence of the existence of tuberculosis. Roentgenologically, the presence of a cold abscess specifically identifies the process as tuberculous.

Although tuberculous arthritis occurs most frequently in childhood and young adult life, it may affect the aged also; "senile scrofula" was the name given it by Sir James Paget. Darling [75] felt that an arrested or active pul-

monary tuberculosis has the power in old age of instituting a tuberculous arthritis that runs a different clinical course from that seen in adolescence, and that such a senile tuberculosis is likely to be mistaken for hypertrophic osteo-arthritis. In early stages its differentiation from hypertrophic arthritis, he feels, may be possible. It begins with slight pain, stiffness, synovial swelling, and a limited effusion, and it may be associated with atrophy of muscle. Onset of suppuration furnishes an indication for exploration. The diagnosis is made on finding bacilli of tuberculosis in aspirated pus. The progress of the disease is more rapid and the process more destructive than in the young, but in spite of its greater severity in the aged the disease usually runs a less painful course. Darling reported two such cases: that of a man aged 66 years, with advanced pulmonary tuberculosis who had subacute swelling of a knee considered by the roentgenologist to be septic arthritis, and that of a man aged 83 years with an old, presumably inactive apical tuberculosis, who had involvement of an elbow. In both cases exploration revealed pus in which bacilli of tuberculosis were found.

Evaluating various aids to an early diagnosis of tuberculous arthritis, Cooperman [76] believed that biopsy and guinea-pig tests are the most reliable. The significance of the von Pirquet and Mantoux tests is lost with advancing years. Focal reactions with intracutaneous tuberculin are not specific; roentgenograms may suggest tuberculosis when another type is later proved to be present and may be long negative in tuberculous joints. An illustrative case was given: that of a boy 13 years old who developed monarticular arthritis of a knee. Six months later roentgenograms were still essentially negative. A roentgenogram of the chest showed infiltration of one upper lobe. The Mantoux test was positive. Examination of aspirated material by direct smear was negative but the guinea-pig test was positive for tuberculosis. Exploration of the knee confirmed the diagnosis.

Ordinarily, for reasons not well understood, tuberculous arthritis involves but one joint; in some cases, however, two or more joints may be involved. Nevertheless chronic monarthritis is so characteristic of tuberculosis that when a patient presents himself with such a condition, tuberculous arthritis is generally first considered, and when more than three joints are the seat of arthritis the probability of tuberculosis being the etiologic agent is considered remote. Ghormley and Brav,[77] in a series of 168 cases of tuberculous arthritis of the knee, noted involvement of two joints in 22 cases (13 per cent), of more than two joints in nine cases (5 per cent). Twenty of 24 cases of monarticular involvement thought to be tuberculous were later proved by A. D. Smith [78] to be otherwise. Joints involved were: the knee in 18 cases, hip in four, elbow in one, and tarsus in one. The ages of the patients were 19 months to 35 years, averaging 14.5 years. The duration of symptoms (a few months to 10 years), and the involvement of only one joint, were suggestive of tuberculosis. The joints presented characteristics which have been considered classic for tuberculosis but which Smith

felt were just as common in non-tuberculous arthritis, that is, monarticular involvement with swelling but with little tenderness or heat, with limitation of motion from muscle spasm and atrophy of adjacent muscles. Roentgenograms suggested a diagnosis of tuberculosis in five cases; in others the findings were indefinite and variable; but so they may be even in proved tuberculous arthritis. The tuberculin test was positive in 9 cases, doubtfully positive in three, and negative in eight. Exploration of the joint was done in each instance; the objective appearance of joint tissue conformed to that seen in many cases of synovial tuberculosis: a moderate excess of clear, yellow synovial fluid, synovial proliferation, and pannus formation. The pathologic sections, however, did not show tuberculosis in any case, the picture varying from that of an acute to that of a chronic inflammatory process. Cultures of tissue were generally negative. Guinea-pig tests were done in 22 cases and were negative. This test, the author felt, was not very useful because the results cannot be learned for six weeks and it is inconclusive if negative.

Smith concluded that: (1) cases of monarticular chronic arthritis are often not tuberculous but of a "nonspecific type," simulating tuberculous arthritis in many respects, (2) it is often impossible to differentiate these lesions from those of tuberculosis by physical or roentgenologic examination, (3) laboratory tests are often not helpful, although a repeatedly negative Mantoux test is suggestive, and (4) aspiration of joint fluid and the guinea-pig tests are not as useful as biopsy, which gives information immediately available and which is the only certain method of making the diagnosis. Even so, the gross appearance of the joint may suggest tuberculosis, but the pathologic sections show nontuberculous inflammatory changes.

"Tuberculous Rheumatism." This is an entity which has never received general recognition in this country but which has gained acceptance in Europe, particularly in France. Poncet, in 1897, described the condition under the term "rheumatisme tuberculeux." His views have been modified and extended somewhat by others. The term "tuberculous rheumatism," as used by its proponents, designates a form of polyarticular disease distinct from tuberculous arthritis yet also related to a tuberculous infection. Whereas in tuberculous arthritis viable bacilli of tuberculosis are found or presumed certainly to be present, in tuberculous rheumatism their presence in joints is not necessarily presupposed. The disease "tuberculous rheumatism" is thought to result from the action of diffusible toxins, an allergic reaction to bacilli of tuberculosis elsewhere, an ultravirus of tuberculosis, to attenuated bacilli, or to trophic changes coincident with tuberculosis elsewhere in the body. The clinical picture of "tuberculous rheumatism" is supposed to resemble in one case atrophic arthritis, in another hypertrophic arthritis, and in still another acute rheumatic fever so closely that it is clinically indistinguishable.

Ory[79] and Cooperman[80] favor the acceptance of such an entity, have renewed the arguments in its favor, and suggest that it is not uncommon.

Cooperman studied four cases of atrophic polyarthritis believed by him to be "proved tuberculous polyarthritis" (i.e., tuberculous rheumatism); on clinical grounds alone they were indistinguishable from "infectious arthritis of known etiology." It is distinguishable from streptococcal arthritides, however, after a study of its evolution, clinical behavior, anatomic and pathologic structure, and roentgenographic alterations. All four of his patients had pulmonary tuberculosis; in one case there were bacilli of tuberculosis in the sputum, in another a positive guinea-pig test. Biopsy was done in all four cases. In two of the cases, swelling and vacuolization of the intima of blood vessels, giant cells, necrosis, and endothelial cells were found, the preponderance of endothelial cells and edematous infiltration being the characteristic feature. In two other cases tissue from knee joints revealed "typical tuberculous pathologic changes." In some cases, however, the articular lesions did not show the specific picture of giant cells and tubercles, the cytologic picture could not be distinguished from that of ordinary inflammation, and biopsy and guinea-pig inoculation were necessary to prove the relationship of tuberculosis.

Ory was of the opinion that various species of tuberculous rheumatism are larval expressions of tuberculosis, arising in persons infected with but few bacteria, or with a weakened virus, or great bodily powers of resistance.

(For a further appraisal of this condition the reader is referred to an article which has just appeared and which more properly belongs to our next review: Brav and Hench: Tuberculous rheumatism—a résumé, Jr. Bone and Joint Surg., 1934, xxii, 839–866.—Ed.).

Syphilitic Disease of Joints and Bursae

Syphilitic disease of joints and contiguous structures has been reviewed by Kling [81] and O'Reilly.[82] The literature would indicate that syphilitic arthritis can imitate every form of joint disease, and that it occurs in from 2 to 20 per cent of cases of syphilis. In cases reported the condition has resembled acute febrile infectious arthritis, atrophic, or hypertrophic arthritis. Monarticular and polyarticular forms are noted, from a simple effusion to gummatous granulation and finally to destructive processes with deformity and ankylosis. Symptoms are usually less notable than pathologic findings. Pain may be absent or slight and it is often nocturnal (O'Reilly). Congenital syphilitic diseases of joints are more common than acquired types and include osteochondritis, with secondary synovitis, simple synovitis, single osteo-arthropathy, usually with night pain or gummatous affections of synovia. Acquired syphilitic disease may be marked by frequent arthralgia, synovitis, and hydro-arthroses, or gummatous arthritis, perhaps secondary to osteitis. O'Reilly cited five representative cases, all with positive Wassermann reactions, and all clearing completely or markedly during specific treatment: a case of painful feet, two of polyarthritis simulating atrophic arthritis, and two of hydro-arthrosis. The results of therapy help to verify the presumption of the syphilitic cause of the condition.

In 112 cases of arthritis with effusion Kling discovered nine which he diagnosed as syphilitic: seven of simple synovitis, one of synovitis and juxta-articular gumma, and one of synovitis with osteochondritis and periostitis. All occurred in the late stage of infection. The Wassermann reaction on joint fluid as well as blood was strongly positive in eight cases, weak in one. A search for syphilis should be made in cases of involvement of one or both knees, with only slight pain, muscle spasm, and periarticular thickening without systemic manifestations. Rigid technic is required to avoid false Wassermann reactions on joint fluid. Kling does not accept positive Wassermann reactions in joint fluid as conclusive proof of the nature of the disease, but a positive reaction in joint fluid with a negative reaction in blood is suggestive, and a negative reaction in joint fluid of a known syphilitic is by itself proof of the nonsyphilitic etiology of the arthritis. Therapeutic evidence is important and is based on the inefficiency of nonspecific, and a characteristically successful response to specific, therapy. Marked and prompt restoration of joint function may ensue, as occurred in the case of Keefer and Myers [83] in which there was subacute febrile polyarthritis, painful lymphadenopathy, and maculopapular syphilids.

Syphilitic Bursopathy. Only 34 cases are recorded, according to Morrissey and Reynolds,[84] who discuss a case of ulcerating patellar bursitis associated with cutaneous syphilitic ulcers.

"Charcot Joints." This term refers to enlarged, relatively painless, hypermobile joints of neuropathic origin which occur most commonly in tabes dorsalis but also in syringomyelia. In recent reports its usual characteristics are reviewed. A case of syphilitic Charcot's disease of a hip continued to progress in spite of intensive specific and nonspecific treatment by Hunsaker.[85] Collapse of the fifth lumbar vertebra occurred in a tabetic patient seen by van Nostrand and Baillie.[86] Warfield [87] observed three patients with Charcot's disease of an elbow joint: two with tabes and one with syringomyelia.

Rarer Types of Specific Infectious Arthritis

Typhoid arthritis is reported as a complication in from 1 to 12 per cent of cases of typhoid fever. It may be polyarticular or monarticular. Recovery of joint function or ankylosis may occur. Occasionally suppuration is produced. Typhoid arthritis occurred in two of 161 cases of typhoid fever seen by Keller.[88] Typhoid spondylitis is one of the less common varieties. A number of cases of spondylitis in which roentgenograms simulated "typhoid spine" were seen by Woldenberg [89] among veterans who had never had typhoid fever but who had received typhoid inoculations. No relationship could be proved, however. (The data are meager, but roentgenograms and descriptions suggest ordinary varieties of spondylitis.—Ed.).

Arthritic complications are listed as occurring in certain exotic diseases:

dengue, melitococcosis, undulant fever, Bang's disease, certain spirochetal infections such as sodoku and yaws, and leprosy. (Labendzinki, 1931.) In association with undulant (Malta) fever, Kulowski and Vinke [90] saw an instance of spondylitis and O'Donoghue [91] one of septic arthritis of a hip. In the first case low back pain began two months before the onset of fever. Roentgenograms showed destruction of lower lumbar interarticular facets. A large abscess was opened, yielding cultures of *Brucella melitensis*, bovine variety. In the second case chills, fever, and pain in a hip appeared seven weeks after the onset of the initial fever. The hip was drained and from thin pus specific organisms were cultured. A solid ankylosis resulted. Blood agglutinations were positive in both cases, 1 : 320 and 1 : 160.

Haverhill Fever. In 1926 an epidemic of acute febrile polyarthritis ("erythema arthriticum epidemicum"), associated with a rash, appeared in Haverhill, Massachusetts. The clinical features, described by Place, Sutton and Willner (1926), included polyarthritis appearing on the first to fourth day of illness. In some cases joints were only mildly attacked; in others marked swelling, redness, and hydrops appeared for 3 to 14 days. A specific organism, "Haverhillia multiformis," was isolated from the blood. (Parker and Hudson, 1926.) An isolated case is described by Hazard and Goodkind.[92] The source of infection is unknown but may be from milk. Specific agglutinins are present. Crippling may be marked for a time but recovery of joint function tends to recur in one to two months. (See also Place, E. H., and Sutton, L. E.: Arch. Int. Med., 1934, liv, 659–684.)

"Madura Foot." This should not be classed as a form of arthritis, as all structures are involved, skin, soft tissues, joints and bones. It is of interest to note, however, that acute, and later chronic, granulomatous arthritis developed in rabbits injected by Gammel and Moritz [93] with Monosporium apiospermum, establishing the pathogenicity of the fungus. Synovia, cartilage, bone, and periarticular soft tissues were involved. Abscesses and granulomas developed.

Rheumatic Fever

Incidence. Some (Poynton and Schlesinger, 1931) state that there has been considerably less rheumatic fever since the World War. In New York the rate apparently was definitely declining between 1906 and 1919 (Lambert, 1920). Studying the yearly incidence in two New York hospitals, where 1,152 cases of rheumatic fever have been encountered since 1897, Davis [94] noted a decline from 1897 to 1919, a rise since 1919. Rheumatic fever follows a cycle in incidence and virulence similar to that found in many acute infectious diseases. In rheumatic fever the cycles are of three to five years each.

Since rheumatic fever and rheumatic endocarditis are usually not reportable diseases, we have no satisfactory mortality statistics, at least in the United States. In England, 250,000 out of 5,000,000 school children suf-

fer from "rheumatism" (Clarke [95]). Most European writers state that rheumatic fever is chiefly a disease of the poor, being 20 to 30 times more frequent among them than among those of the upper classes. Since but few data are available regarding the social incidence of rheumatic fever in this country, Paul and Leddy [96] studied the incidence of rheumatic carditis at Yale University, examining health records of undergraduate and graduate students who attended the university between the years 1920 and 1930. Such a group represents a selected number of young men mostly from the northeastern part of the country and mostly from the upper economic strata. The incidence of rheumatic heart disease among 7,914 undergraduates was found to be only 8.2 per 1,000, as compared with 15 per 1,000 the average figure obtained from statistics of comparable age groups (18 to 25 years) of the general male population in the same locality. The incidence among the 4,455 graduate school students was 11.4, an incidence somewhat higher, possibly due to the fact that a smaller percentage of the graduate students came from homes of means. Among undergraduates who had attended expensive boarding schools the incidence was only 5.8 per 1,000 as compared with 12.5 per 1,000 for those from high schools. These studies thus support the contention that rheumatic fever is a disease that has a lower incidence among people of ample means. From the control studies of Paul and Leddy, however, it appears that the factor of poverty does not have as important a predisposing rôle in determining the incidence of rheumatic fever or rheumatic carditis as it does in tuberculosis.

Considering the question of economic status as a predisposing factor, Davis compared the curve of yearly incidence of rheumatic fever in a New York hospital population to the curve of retail commodity prices in the United States and was unable to conclude that fluctuations in economic welfare produced by "boom years" and depression had any influence on morbidity due to rheumatic fever. Plotting the curve of incidence beside that of the annual rainfall in New York City, he concluded that wet weather was a definite factor in increasing its prevalence.

Climatic conditions and geographic location are said to influence markedly the incidence of rheumatic fever. McLean [97] believed that these factors influence the clinical manifestations of rheumatic fever more than the general incidence of the disease. It seems to be more common and more severe in the colder parts of the temperate zones than in the warmer parts, and it is extremely uncommon in the tropics. It is rare in Louisiana and Georgia, and half as common in Virginia as in Massachusetts. Longcope (1931) noted that rheumatic fever in Baltimore is not associated with the severe arthritic manifestations that he saw in New York. However, in Baltimore it is characterized by rheumatic carditis of insidious onset and mild exacerbations, and is as relentless in its progress toward destructive carditis. In Birmingham, McLean [98] noted a similar state of affairs, rheumatic fever there being a disease primarily of the heart, characterized by an insidious onset, with cardiac involvement out of proportion to the moderately

severe and relatively infrequent arthritic and choreic manifestations. Based on admissions to the Children's Hospital, the general incidence rate was 1.79 per cent, being 3.6 per cent at the age of five years. Girls were 14 per cent more susceptible than boys. Arthritis occurred in only 22 per cent of 122 cases. A diagnosis of carditis was made in 83.6 per cent of cases. In Birmingham, the incidence of arthritis is 46 per cent less, of chorea 26 per cent less, of cardiac disease 4 per cent greater, than in New York City. The incidence of rheumatic carditis without a history of other clinical manifestations of rheumatic fever was 50 per cent greater in Birmingham than in New York, and children apparently developed rheumatic infection and its cardiac complications at an earlier age in Birmingham than in New York. (These statistical differences are striking and should be verified elsewhere. It has been felt that if one were to have rheumatic fever, it would be better to have it down South. It would appear that although there may be less rheumatic fever in the South than in the North, when one does have it geographic location may actually be detrimental. For rheumatic fever, in part deprived of its dramatic warning signals of acute arthritis, chronic muscle pain, or chorea, may in the South escape diagnosis and early treatment which it might have elsewhere. Thus the insidious progress of rheumatic carditis may be favored.—Ed.)

To evaluate hereditary or constitutional factors, Irvine-Jones [99] studied the incidence of rheumatic fever in 500 families in Toronto and St. Louis, including 800 rheumatic persons in immediate family circle. Nonrheumatic families were also studied. Thirty-two per cent of the rheumatic families both in Toronto and St. Louis showed multiple instances of rheumatism. When a member of a family exhibits the clinical manifestations of rheumatic fever, the chance of its appearing in other members of the family is practically doubled. It was more common in more distant relatives in rheumatic families than among those of nonrheumatic families. Studying a small group of 20 persons who were actually living in close contact, it was found that the disease occurred among about 25 per cent of the unrelated boarders and among 65 per cent of those who were related. It simultaneously affected both twins of two pairs of identical twins but only one of each of eight pairs of nonidentical twins. It was more common in families where the father was affected. It tended to occur among blonds and red-haired persons. The greater susceptibility of girls to the disease was found chiefly in families in which the father was rheumatic. H. C. Jamieson [100] noted the familial tendency of rheumatic fever to appear among cousins.

Course and Symptoms. Various terms have been proposed in place of "acute rheumatic fever," to withdraw emphasis from an acute or a febrile stage, from the arthritic or carditic phases alone, and to include under one designation the various connected manifestations of the rheumatic syndrome. H. C. Graham [101] has proposed the term "rheumaticosis" to designate the process as a long-continued, low-grade, all pervading indolent toxicosis primarily responsible for the insidious prodromes as well as for the more

frank characteristics of the disease, that is, tonsillitis and pharyngitis, chorea, arthritis, nodules, and carditis. With similar intent, Coburn [102] uses the term "the rheumatic state." Dally [103] favors Cheadle's (1889) term "the rheumatic series." Sigler [104] reviewed the chief features of rheumatic fever. While the heart is the organ most often and most seriously affected, no organ of the body may escape the essential lesions of this state, namely, the submiliary node or Aschoff body, a small round-cell infiltration about minute blood vessels, especially in the muscular, nervous, and the osseous systems.

Depending on what tissue is most severely affected, rheumatic fever presents the following clinical forms: (1) cardiac, (2) arthritic, an uncommon spinal form sometimes being characterized by stiff neck and a positive Kernig sign, which with fever and leukocytosis may simulate meningitis, (3) muscular, which is the most frequent form, next to the arthritic, and of which "growing pains" and a mild fever, possibly with slight carditis, may be the signs, (4) nervous, with chorea and occasionally "cerebral rheumatism," (5) pseudosurgical, in which rheumatic fever may be ushered in with relatively acute but indefinite abdominal symptoms for which operation has been erroneously advised and in which the typical symptoms of rheumatic fever appear later, and (6) septicemic, characterized by unexplained fever, fleeting pains, malaise, headache, drowsiness, weakness and occasional rash, all lasting for some weeks or more and the nature of which may be clarified by the later appearance of nodes, otherwise unexplainable pleural exudates and partial response of symptoms to salicylates.

Natural Course of the Disease Untreated. Many false deductions are made as to the efficacy of certain measures in cases of rheumatic fever because so few careful observations have been made on the natural course of the untreated disease. No specific treatment and no antipyretics were given to a group of 105 patients who were studied by Graef, Parent, Zitron and Wyckoff [105] over a period of two years. One such group was affected chiefly by polyarthritis, another by chorea, another by structural carditis. Forty-seven patients were followed to the point where there was cessation of activity, evidenced by normal temperature, pulse rate, and leukocyte count, freedom from such heart signs as gallop rhythm, prolonged P–R interval or other significant electrocardiographic signs and pericardial friction, freedom from evidence of pulmonic or pleural infection, from choreiform movements, and from subcutaneous nodules or rashes. Patients were dismissed when they were considered "normal" for 2 weeks after the last signs of activity. Striking spontaneous remissions in temperature and arthritis occurred. The severity and duration of the disease corresponded well with that of patients who were treated. Six patients who had previously had severe rheumatic carditis died. The remaining 41 patients enjoyed spontaneous cessation of the disease. Graef and his colleagues concluded that the worth of "specific therapy" (tonsillectomy, salicylates, etc.) has not been proved and that an evaluation of any further treatment must be based on a comparison with such a basic study as is here reported.

Recent clinical summaries and observations on rheumatic fever are those of Burnett,[106] Gray, Fendrick and Gowen,[107, 108] Meakins [109] and Cecil.[110, 111] Two new series of cases are analyzed. McLean [97, 98] reviewed the early manifestations of the disease in 258 children. Brooks and O'Regan [112] studied its onset in 700 residents of New York City of all ages. Of McLean's patients 126 were girls, 132 boys. In general, they were pale, high-strung, nervous, irritable children who were easily fatigued, had poor appetites, and who were either losing weight or were not gaining it as they should. The onset of the disease was between the ages of two and five in 75 cases, five and seven in 86 cases, and after seven years in 97 cases. Eighty per cent gave a history of repeated tonsillitis and 50 per cent had tonsillar infection. Dental infection was present in 19 per cent of cases, sinusitis in about 8 per cent. Joints were involved in 68 per cent, chorea was noted in 27 per cent, and paroxysmal abdominal pains were noted in 28 per cent. Constant systolic murmurs were found in 78 per cent of cases. Anemia and underweight were frequent. Only three patients had nephritis, and one pyelitis. The onset of the disease was between January and April in 58 per cent of the cases. The incidence and severity of respiratory infections during the first five years of life were apparently no greater in rheumatic than in nonrheumatic children.

In New York City the diagnosis of rheumatic fever should present no difficulties, as Brooks and O'Regan felt that its mode of onset is highly characteristic, with a very distinctive type of arthritis and almost invariably early cardiac involvement. Of 700 patients, 443 were males and 257 females. Fifty patients were in the first decade, 140 in the second, 210 in the third, 171 in the fourth, 88 in the fifth, 26 in the sixth, 9 in the seventh, and 6 in the eighth decade of life. The most frequent prodromes were infections of the upper respiratory tract. The tonsils were considered infected in 382 cases, the teeth in 238 and the sinuses in 33. Adenitis appeared early in 187 cases. All patients had fever but only 65 had chills in the early stage; 622 had the characteristic migratory, acute polyarticular periarthritis. Monarthritis was rare; when it occurs, rheumatic fever is not the likely diagnosis. Various skin manifestations, considered allergic, were encountered in 42 cases. Renal involvement was very rare. Sixty-three had early evidence of pulmonary, bronchial, or pleural disease. Cardiac involvement was exceedingly frequent, being noted early in 493 cases, eventually in 606. (The authors said: "Sixty-two cases were complicated by certain or possible gonococcal infection. . . . The two forms of arthritis may unquestionably be associated in the same case." In view of the fact that gonorrheal arthritis is so frequently preceded by a stage of fleeting polyarthralgia, one might consider this statement critically and wonder if some of the cases thus noted were not in reality gonorrheal arthritis, not rheumatic fever.—Ed.)

Schwarz [113] presented an unusual case of rheumatic fever, the patient being a child of 17 months. A complete clinical and pathologic study of the first attack was given. The attack proved fatal one month after the onset.

The disease ran a fulminating course, presenting clinically only fever, tachycardia, and pain in one joint. Its true nature was not suspected. The main pathologic lesions were cardiac: inflamed valves, coronary thrombosis, myocardial infarction, lesions in the auricles and in the pulmonary artery.

Laboratory Data: Sedimentation Rates, Blood Counts, Electrocardiograms. Data on other than routine laboratory tests will be discussed later under studies on etiology and pathogenesis.

Further evidence is given that changes in the sedimentation rate are almost parallel with the varied progress and clinical alterations of the disease. (Payne,[114] Bach and Hill,[115] and Poynton.[116]) The test distinguishes between a false improvement, due perhaps to salicylates, and one due to recession of the disease. It provides a numerical gauge to the patient's progress, good or bad. Its persistent failure to return to normal, when fever and joint pains subside, is highly suggestive of the continued presence of active pathologic changes, such as a cardiac lesion. It may aid in deciding whether bed rest can be terminated. The rate is, however, uninfluenced by the degree of cardiac injury, from a quiescent lesion. Payne has modified the usual technic, utilizing 0.4 c.c. of blood from one stab of the finger as being more practical for children.

It has been shown that a study of frequently taken electrocardiograms demonstrates disturbances in a high percentage of cases of rheumatic fever. (Cohn and Swift, 1924; Rothschild, Sachs, and Libman, 1927.) Master and Jaffe,[117] who made daily electrocardiographic studies in 63 cases, found definite evidence of myocardial involvement in 100 per cent of the cases. The changes found were increased auriculoventricular conduction time, auricular fibrillation or flutter, heart block, R–S–T abnormalities, T-wave inversions, and widening and notching or slurring of the Q–R–S group. Since patients with atrophic arthritis showed no such changes, electrocardiographic alterations in a given case would suggest rheumatic fever rather than acute atrophic arthritis.

Pathologic Studies and "Complications": Specific Granuloma. Cytologic studies of the characteristic cell of the rheumatic granuloma have been made by McEwen.[118] At present much uncertainty exists as to the nature and origin of the large basophilic, and often multinucleated, cells of the Aschoff body, and as to whether they originate from muscle cells, endothelial cells, connective tissue cells, or wandering or fixed phagocytic cells. McEwen examined them with supravital stains, a method previously used successfully in identifying cells in the lesions of tuberculosis and syphilis. As cells of the Aschoff body and cells of the rheumatic granuloma are essentially identical, and as rheumatic nodules are easily available and more readily handled than Aschoff bodies, nodules were studied on the assumption that conclusions drawn from them would apply equally to Aschoff bodies. The importance of establishing the nature of these cells in the Aschoff body and in the rheumatic granuloma lies in the occurrence of somewhat similar nodules in other diseases; such as syphilis, yaws, acro-

dermatitis chronica atrophicans, scleroderma, and especially atrophic arthritis. Scrapings of subcutaneous nodules from 10 patients with rheumatic fever were examined, also control material from various sources. They showed a great predominance of certain cells almost devoid of phagocytic power and not characterized by the reactions with neutral red that distinguish monocytes, epithelioid cells, and clasmatocytes. Hence they differ from the essential cells of the lesions of tuberculosis and experimental syphilis. These differences are probably of a functional and developmental, rather than of a genetic, nature. The cells probably arise from undifferentiated mesenchymal elements of loose connective tissue, although it is possible that endothelial cells take part in their formation in some instances.

Subcutaneous Nodules. Subcutaneous nodules of rheumatic fever are closely related to, if not identical with, those found frequently in atrophic arthritis. They are highly characteristic of the two diseases, and suggest to Dawson [119] that the two may represent different phases of the same fundamental pathologic process. Such evidence, however, is presumptive and by no means constitutes proof of an identical cause.

Lymph Nodes. The presence of Aschoff bodies in hyperplastic nodules in the superior mediastinum (regional nodes that drain organs affected by the disease) seemed to Fraser [120] to provide further evidence that the virus can pass from infected tissue into the blood stream via lymph channels.

Hemorrhagic Changes. In addition to the characteristic perivascular (Aschoff) lesions of rheumatic fever, Coburn [102] considers another lesion to be of rheumatic origin, because, although it has no distinct histologic appearance, it develops simultaneously with specific lesions and occurs at the height of the disease's activity, the first two weeks of an attack. Examination of 100 patients who died from rheumatic fever demonstrated the usual lesions; but it also demonstrated innumerable hemorrhages: scattered purpura in the peritoneal cavity, lungs, ovaries, suprarenal glands, spleen, kidneys, over the sigmoid, in the mesentery, in the tricuspid, mitral, or pulmonary valves, in the ventricular endocardium, and in the white matter of the brain. The lesions are hemorrhagic; capillaries are dilated. Edema, but no detectable alteration in blood vessels, is present. They probably result from alterations in vascular permeability, with diapedesis, injury to mesodermal tissues, and resulting inflammatory reaction. In one case they were associated with acute renal insufficiency, in others with mania, with cutaneous lesions, and with asphyxia from hemorrhagic solidification of the lungs. In three cases the hemorrhagic areas were probably responsible for acute abdominal symptoms, for which operation was done at the onset of the rheumatic fever.

Cardiac Alterations. Coombs,[121] reviewing rheumatic heart disease, stated that the myocardium and the mitral valve are involved in 100 per cent of cases of rheumatic fever, the pericardium in 60 per cent, aortic valve in 50 per cent, and tricuspid valve in 30 per cent. Appreciation of the enormous morbidity and mortality produced thereby is still growing (Cecil,[110]

Sloan [122]). Forty per cent of all cases of heart disease, the cause of more deaths in the United States than any other condition, are of rheumatic origin (McLean). During the past 50 years deaths from heart disease in the United States have increased 42 per cent, whereas those from tuberculosis have declined 44 per cent (Burnett [106]). In England, 1,500 deaths a year are due directly to rheumatic fever, more than 20,000 deaths a year are due to rheumatic carditis, and at any one time 140,000 people in England are suffering from rheumatic carditis (Clarke [95]). Coombs [123] noted that about 32 per cent of cases of heart disease in private practice were of rheumatic origin. There was five times as much rheumatic heart disease among children in Bristol, England, as in surrounding rural areas.

Usually the earliest clinical indications of valvular injury are, according to Coombs, muffled apical sounds, which probably denote edema of the mitral or aortic leaflets, and the gradual onset of murmurs. The early signs of cardiac inflammation may be trivial and their existence doubtful, the impulse a little wider to the left than it should be, the first sound at the apex weak and impure. Within a few days this grows into a true apical systolic murmur, and the second sound at the pulmonary area becomes louder. In severe cases there may be pericardial friction, an aortic diastolic murmur, and electrocardiographic changes. In about a fourth of cases these signs gradually recede after a few days, disappearing within a year under prolonged treatment.

We cannot enter deeply into a discussion of rheumatic heart disease, a field adequately covered elsewhere. Three studies will be mentioned. In 5,215 consecutive necropsies, 474 cases of rheumatic heart disease (9.1 per cent) were found by Davis and Weiss.[124] Rheumatic carditis was directly responsible for death in 35 per cent of these 474 cases; it was contributory in 8.6 per cent. Malignant endocarditis was associated with rheumatic heart disease in 4.4 per cent of the cases. In 229 cases deaths from rheumatic carditis were distributed widely from the second to the fifth decades of life, the largest number occurring in the fourth or fifth decades. Forty of 47 persons who had subacute bacterial endocarditis superimposed on rheumatic heart disease died before the age of 50. In all of 19 cases with malignant endocarditis superimposed on rheumatic heart disease death occurred before the age of 40. Rheumatic heart disease is frequently present with cardiac signs and symptoms as late as the seventh decade of life.

In a given case, a favorable prognosis may, according to Poynton,[116] be entirely altered by renewed activity. Mortality is higher among boys, varies in both sexes in different years, but is greater when carditis occurs before five years of age. In children, 30 per cent die in the first attack. If mitral stenosis occurs before the age of 12, the prognosis is bad. The presence of fever is not important as a guide to the severity of carditis, but nodules are of serious import; they were present in 27 of 72 fatal cases.

Observations over a period of 10 years have been made on 450 children with rheumatic heart disease by Stroud, Goldsmith, Polk and Thorp.[125]

The average age at onset of rheumatic fever was 7.3 years. Of 307 children for whom records were complete, 41 per cent are dead or totally disabled, 59 per cent are able to work or go to school. A familial incidence at least as high as that of tuberculosis seemed apparent, with Italians and Hebrews more susceptible than those of American or Irish parentage. Sixty-one per cent of 428 attacks of rheumatic fever occurred between December and May, the greatest number in March. The location or number of valves involved had less to do with prognosis than the virulence of the infection, resistance of the host, and number of reactivations.

De la Chapelle and Graef [126] reported a case of polyserositis (Pick's syndrome) with rheumatic valvular disease, unusual in that it occurred without adherent pericarditis. Polyserositis during the course of rheumatic fever is rare.

Pleurisy and Pneumonia. Pulmonary manifestations arise insidiously but rather commonly in severe rheumatic fever. It has been recognized for 200 years that lungs and pleura may be attacked by the rheumatic virus (Gouley and Eiman [127]; March 1927). Further data on incidence, and on chemical and pathologic characteristics of these pulmonary lesions, are presented (Gouley and Eiman,[127] Howard,[128] and Myers and Ferris [129]).

The symptoms of "rheumatic pneumonia" are not spectacular, an initial chill does not announce the pulmonary invasion, and a cough may or may not be present. Its physical signs are more prominent, but they must be sought as they may last only a few days, and its consolidations are transient. Râles may be absent during the stage of consolidation (Howard). Gouley and Eiman described the pathologic changes in nine cases. Such lungs are grossly different from those affected by common pneumonia. The pulmonary lesions show histologic characteristics identical with those of rheumatic fever elsewhere: focal perivascular lesions, necrotic and proliferative areas of the Aschoff type, vascular injury, rupture of capillaries with liberation of fibrin, endothelial hyperplasia, and an interstitial perivascular exudate of large endothelial cells. In areas of necrosis, polymorphonuclear cells are scarce. The consolidated areas, of India-rubber consistence, are not atelectatic as has been stated.

Rheumatic pleurisy occurs in 2 to 20 per cent of cases of rheumatic fever and, next to carditis, is one of the most frequent complications of the disease. Its pathologic characteristics are described by Howard, and by Myers and Ferris. Ten of the 15 patients of Myers and his colleagues had pleural effusions; three had fibrinous pleurisy, two had bilateral hydrothorax. Clinical characteristics were sudden onset, dyspnea, mild cyanosis, pain and increased temperature. The fluid of rheumatic pleurisy was noted for its hemorrhagic nature and the readiness with which its formation took place. Salicylates did not alter the course of pleural or pulmonary lesions (Myers and Ferris).

Kidneys. Contrary to the experience of some (McLean, Brooks and O'Regan) who say that renal lesions rarely occur in rheumatic fever, acute

nephritis is said to occur in from 10 to 20 per cent of cases according to others (Gray, Fendrick and Gowen) who say, however, that it does not lead to chronic glomerulonephritis. In view of these statements a report by Shambaugh,[130] on uremia in a case of rheumatic fever is of interest. A young man entered the hospital in a state of circulatory collapse and marked dehydration; neither pulse nor blood pressure could be felt for two days. Almost complete anuria was present, but examination of a few cubic centimeters of catheterized urine showed it to be normal. Blood urea rose to 119 mg. per 100 c.c. Recovery followed appropriate therapy. Shambaugh assumed that uremia occurred in the absence of nephritis, chiefly because of an anuria from hypotension.

In 22 per cent of cases of rheumatic endocarditis a diffuse glomerulitis was observed by Bell [131]; in 3 per cent an embolic type of glomerulitis was found, percentages much higher than previously reported. Baehr and Schifrin [132] found diffuse glomerulonephritis only three times (1.3 per cent) in 235 cases of rheumatic endocarditis at necropsy. Its rarity as a complication of rheumatic fever is in contrast with its frequent occurrence following various diseases of proved streptococcal origin. The appearance of nephritis justifies review of a case to make certain of the diagnosis. Baehr and Schifrin believed its occurrence may indicate the bacteria-free stage of subacute bacterial endocarditis, Libman's verrucous endocarditis (nonrheumatic), or periarthritis nodosa rather than rheumatic fever.

Etiology and Pathogenesis. The cause of rheumatic fever has not been determined. There are three general theories: (1) the infectious theory, (2) the endocrine theory, and (3) the metabolic or chemical theory. The majority favor one of the variants of the infectious theory, of which there are three: bacterial, parasitic and virus.

Bacterial Variant of the Infectious Theory. The editors of this review approach with considerable trepidation the task of elucidating present conceptions regarding this variant. It is difficult to interpret studies which the workers often frankly admit they do not themselves fully understand. It is almost impossible to compare results of different workers because of differing technic. Furthermore, the nomenclature of bacteriology and immunology is none too well established. Nevertheless, it is important to be familiar with some of the details of this work even if one makes no claim to special bacteriologic knowledge.

To follow the bacteriologic studies on rheumatic fever (as well as on atrophic arthritis) it will be helpful to visualize the data in table 2 which summarize the further subvariants of the bacterial theory and the names of a few of the men identified therewith. No attempt has been made to approach completeness as far as names are concerned. In brief the three subvariants of the bacterial variant of the infectious theory are these: (1) Rheumatic fever is the result of bacterial infection, a bacterial dissemination to affected tissues by way of a bacteremia of varying degree and persistency, the blood stream becoming infected either from an acute or chronic focus.

TABLE II

The Bacterial Variants of the Infectious Theory of Rheumatic Fever
An approximate outline of current opinion
(Many other names might be added; these are representative)

I. Bacteremic variant; the idea of general and direct bacterial infection:
  (*a*) Group-specific; with one species of organism
    1. Bacillus: Bertrand (1928)—Achalme's anaerobic bacillus
    2. Diplostreptococcus: Poynton and Paine (1900)—"*Diplococcus rheumaticus*"
    3. *Streptococcus viridans:* Cecil, Nicholls and Stainsby (1929)—"typical strain"
       Gray, Fendrick, and Gowen (1932)
    4. *Streptococcus hemolyticus*
    5. *Streptococcus nonhemolyticus* (indifferent)
  (*b*) Not group-specific, i.e., with more than one type of streptococcus (as far as hemolysis is concerned):
    1. "Generally," *Streptococcus viridans:* Rosenow (1913), Swift and Kinsella (1917)
       Clawson (1925)

II. Toxemic variant; the idea of "bacterial intoxication" (theory of toxemia without, necessarily, bacteremia):
  (*a*) Group (and strain) specific:
    1. Nonhemolyticus streptococcus: Birkhaug (1927)—"non-methemoglobin-former"
       Small (1927)—"*Streptococcus cardio-arthritidis*"
  (*b*) Not group-specific

III. Allergic variant, the idea of bacterial allergy (the response of tissues hypersensitive to bacteria, the onus being more on tissues than on the inciting germ):
  (*a*) Group-specific:
    1. Hemolytic streptococci: Coburn (1931); Coburn and Pauli (1932). Group-, but not necessarily strain-specific
    2. Other organisms
  (*b*) Not group-specific:
    1. *Streptococcus viridans* and *nonhemolyticus:* Zinsser (1928)
       Swift et al. (1928–1931)
       Birkhaug (1929)
    2. Various streptococci: Clawson (1930)—generally viridans
       Schlesinger (1932)

This is the theory of "bacterial infection," the infection being from (*a*) one specific group and strain of organism, (*b*) organisms that are group, but not strain, specific; * or (*c*) any one of a number of different organisms. For full proof, the bacteremic theory, of course, needs the finding of positive blood cultures, preferably of an individual type or strain of organism in a significantly high percentage, a proof which is, so far, by no means consistently provided. (2) The "bacterial toxemic theory" is that rheumatic fever is due to a bacterial toxemia and not to an actual bacteremia, the toxemia arising from a localized infection with a specific kind of organism or any one of a number of organisms. While positive blood cultures are not to be expected under this conception, the isolation of a specific and identifiable exotoxin is required. The presumed isolation of such a toxin-producer by Birkhaug and Small (1927) has not been confirmed further. (3) The theory of bacterial allergy is that rheumatic fever is due to an allergic reaction to bacteria, a tissue hypersensitivity to bacterial products either from organisms that are group, but not necessarily strain, specific or more likely, a number of different organisms or the nucleoprotein thereof. In this country, streptococci of one variety or another are incriminated almost exclusively, although recently the nucleoprotein of staphylococci has been suspected. Bacilli are thought to be the responsible agents by a few workers in Europe but are here almost totally disregarded.

The chief proponents of the bacteremic theory have been Poynton and Paine (1914), Rosenow (1914), Miller,[133] and Cecil, Nicholls and Stainsby (1929). The chief proponents of the theory of bacterial toxemia have been Birkhaug (1927) and Small (1927). The proponents of the theory of bacterial allergy have been Herry (1914), Faber (1915), Zinsser (1928), Swift and his colleagues (1928–1931), and more recently Coburn (1932), Collis (1932) and Schlesinger (1932). Some who previously supported the first or second theory have since switched to the third.

The basis of reasoning has been studies of throat cultures, blood cultures, cultures of joint tissue, lymph nodes or subcutaneous fibrous nodes, agglutination tests, skin tests, and studies on precipitins, antistreptolysins, and opsonins in blood of controls and of patients with rheumatic fever, and the experimental production of arthritis in animals (table 3).

* The different streptococci isolated are still, in general, classified under three headings (species or groups): *Streptococcus viridans* (alpha or "green" streptococci); *Streptococcus hemolyticus* (beta streptococci), and nonhemolytic streptococci (indifferent, or gamma streptococci). There are of course many different strains (types) of these three species or groups. For example, there are many different strains of hemolytic streptococci; that of scarlet fever, for example, may be different from that of erysipelas, and is presumably quite different from the strain of hemolytic streptococcus isolated in the type of pharyngitis such as that which precedes rheumatic fever. One speaks, furthermore, not only of different strains of hemolytic (or other types of) streptococci, but also of different strains of the hemolytic scarlet fever streptococci (or of different strains of gonococci) of varying virulency. When one uses the phrase "group-specific, but not strain-specific," in referring to the cause of a disease or to agglutination tests, one means that the cause of the disease or of agglutination is just one group of streptococcus (*Streptococcus viridans*, for example, and never hemolytic or nonhemolytic streptococci), but not necessarily just one specific strain, but any one of a number of strains of that group of streptococcus.

TABLE VII

Infectious Theory of Rheumatic Fever
Basis of approval for bacterial subvariants
(The names are but representative)

Test	Results
1. Throat cultures	(*a*) Characteristic: (1) Group and strain specific: Small (1927)—*Streptococcus cardio-arthritidis* (2) Group (but not strain) specific: Coburn (1931)—hemolytic streptococci Coburn and Pauli (1932) Collis et al. (1932) (*b*) Not characteristic: Hitchcock (1928); Nabarro and MacDonald (1929) Graham and Thomson (1932)
2. Blood cultures	(*a*) Characteristic: (1) Group and strain specific: Small (1927)—*Streptococcus cardio-arthritidis* Birkhaug (1927)—indifferent streptococci (2) Group (but not strain) specific: Rosenow (1914)—*Streptococcus viridans* Clawson (1925)—generally *Streptococcus viridans* Cecil, Nicholls and Stainsby (1929) —*Streptococcus viridans* Dawson and Boots (1931)—*Streptococcus hemolyticus* Gray, Fendrick and Gowen (1931) (*b*) Not characteristic: Swift and Kinsella (1917); Moon and Edwards (1917); Coburn (1931); Lichtman and Gross (1932); Collis et al. (1932); Cooley (1932)
3. Joint cultures	(*a*) Characteristic: Generally *Streptococcus viridans:* Cecil, Nicholls, and Stainsby (1929) (*b*) Not characteristic: Numerous: e. g. Dawson and Boots
4. Agglutination	(*a*) Generally characteristic: Small (1927)—Indifferent streptococci; Cecil, Nicholls and Stainsby (1929)—*Streptococcus viridans* (*b*) Generally not characteristic: Clawson (1925); Clawson and Wetherby (1932); Coburn and Pauli (1932); Gray, Fendrick, and Gowen (1932)
5. Skin sensitivity	(*a*) Characteristic: (1) Group specific: Indifferent streptococci, Birkhaug (1927); Kaiser (1928) *Streptococcus hemolyticus*, Collis et al. (1932) (2) Not group specific: *Streptococcus viridans* and indifferent streptococci, Swift, Derick and Hitchcock (1928); Birkhaug (1929) (*b*) Not characteristic: Lazarus-Barlow (1928); Graham and Thomson (1932)
6. Precipitins	(*a*) Present but not specific: Coburn and Pauli (1932) (*b*) Present and essentially specific; some cross precipitation formation—Schlesinger and Signy (1933)
7. Anti-streptolysins	Increased formation (hemolytic)—Coburn and Pauli (1932); Todd (1932)
8. Opsonins	Generally high; Small (1927)
9. Experimental acute arthritis with Aschoff-like bodies	Many results considered positive; others considered not characteristic

Blood Cultures. The chief previous studies are those of Poynton and Paine (1900), Rosenow (1913), Herry (1914), Swift and Kinsella (1917), Suranyi and Forro (1918), Clawson (1925), Small (1927), Birkhaug (1927), Cecil, Nicholls and Stainsby (1929) and Nye and Waxelbaum (1930).

Streptococci, usually of the alpha (viridans) or alpha prime type, have been isolated in 71 per cent of 28 cases of rheumatic fever by Gray, Fendrick, and Gowen. In two cases hemolytic streptococci were isolated early in the attack, and later cultures revealed *Streptococcus viridans.* Considering these differences, these writers felt that cultural standards for the classification of streptococci and the variations of these organisms under different environmental conditions must be taken into consideration. They favor bacteremia and tissue infection as being essential for the production of rheumatic fever, although allergy may play an important part in making joints susceptible. The cultural method used was a modification of that of Cecil, Nicholls and Stainsby, whereby a growth was obtained in one to six days instead of 17 to 30 days; subcultures are avoided. One hundred and thirty-two cultures in 105 pathologic control cases were negative except in 15 instances in which positive blood cultures were to be expected.

Wilson and Edmond [134] obtained positive blood cultures for 46 per cent of 67 children with "acute rheumatic polyarthritis" and for about the same per cent of two control groups consisting of children who were ill of other than rheumatic fever and a group of healthy children. About half of the organisms recovered were streptococci (viridans or indifferent); the others were pleomorphic bacilli. Because the recovery of organisms from both the rheumatic and the control series was comparable, the presence of these organisms in blood cultures of rheumatic children would not seem to be of primary etiologic significance unless one postulates that tissues of the rheumatic child are particularly sensitive to the microörganisms presumably present in their blood. The findings suggested to Wilson and Edmond that bacteria may gain access to the blood stream of healthy and of sick children and are filtered off in various organs where they are destroyed. During illness this transient bacteremia may be increased.

Callow [135] likewise found about the same type and number (53 per cent and 66 per cent) of positive blood cultures in two groups: (1) of 174 patients with rheumatic fever and (2) of 58 persons with acute upper respiratory diseases. A smaller percentage (34 per cent) of cultures from patients with miscellaneous diseases was positive. Eight per cent of 39 normal individuals gave positive cultures. The organisms isolated in the rheumatic group were: *Streptococcus viridans,* nonhemolytic streptococci and pleomorphic bacilli. Under controlled conditions it was possible to transform selected strains of pleomorphic bacilli into diplostreptococci of either the green or the hemolytic type, similar in morphologic, cultural, and biochemical properties to the diplostreptococci isolated from rheumatic and

nonrheumatic patients. A specific etiologic relationship between the isolated organisms and rheumatic fever was questioned.

Cooley,[136] using Clawson's and Cecil's methods, found no significant organisms in blood cultures of 25 children during initial attacks of rheumatic fever. The positive results of Cecil and of Clawson could not be confirmed. A diplostreptococcus similar to that of Poynton and Paine was isolated from blood and pleural effusion in a case of "acute fulminating rheumatic disease" seen by Whitaker[137] who therefore believed that one streptococcus, such as Small's *Streptococcus cardio-arthritidis,* cannot be the sole cause of rheumatic fever. (The patient, a child of three years, had chiefly meningitic symptoms with preterminal pericarditis, cardiac enlargement, and pleurisy. No characteristic polyarthritis is described and there are no postmortem records. The diagnosis of rheumatic fever may be correct but is not proved.—Ed.)

Scudder[138] isolated a higher type of bacterium in cultures of the blood of a young man who died after repeated attacks of rheumatic fever. It was morphologically similar to Streptothriceae, but was later considered related to Mycobacteriaceae. It was also considered a secondary invader but the direct cause of the terminal embolic features.

Agglutination Tests. Clawson and Wetherby[139] were unable to place their patients in such distinct groups as atrophic arthritis, rheumatic fever, and hypertrophic arthritis. They believed that rheumatic fever and atrophic arthritis are closely related clinically, bacteriologically, and immunologically, and that they are the result of an infection, generally with *Streptococcus viridans,* of tissues hypersensitive to such germs. To determine how close an etiologic relationship exists, with Hilbert and Hilleboe[139] they studied streptococcal agglutination in 66 cases in which children had rheumatic fever and in 300 cases of "chronic arthritis." As controls, the serums of 110 normal persons, 46 with scarlet fever, and 20 with glomerulonephritis, were tested. Two strains of streptococcus were used, a *Streptococcus viridans* from the blood of a patient with rheumatic fever, and a streptococcus, which generally produced methemoglobin, isolated from the blood of a person with chronic arthritis. With the rheumatic fever strain, agglutinative titers of the serums of patients with acute rheumatic fever were higher than normal, those of patients with chronic arthritis were not. With the strain from the patient with chronic arthritis, titers were higher than normal in chronic arthritis but especially in rheumatic fever. With both strains titers were decidedly higher than normal in serums of patients with scarlet fever and glomerulonephritis. In all tests, including the normal serums, the chronic arthritis strain was agglutinated in higher dilutions than the rheumatic fever strain, and was apparently more sensitive to agglutination. These findings suggest that rheumatic fever and chronic arthritis are both caused by streptococcal infection but that neither is produced by a specific strain.

Positive agglutination tests to four strains of hemolytic streptococci were found by Keefer, Myers and Oppel[140] in 26 per cent of cases of rheumatic

fever, 54.5 per cent of cases of atrophic arthritis, and 15 per cent of cases of hypertrophic arthritis. No evidence of strain specificity was found. Positive agglutination tests bore no relation to the sedimentation rate or to positive cutaneous reactions to the nucleoproteins of hemolytic streptococci. The agglutinations were of a different order from those described by Tillet and Abernethy [141] for serums of patients acutely ill with various diseases. The exact relationship between streptococcal agglutination and tissue response in cases of rheumatic fever and atrophic arthritis remains undetermined.

According to Hitchcock and Swift,[142] exudates of joints, pleura, and pericardium in both rheumatic and nonrheumatic patients possess agglutinating properties to certain hemolytic streptococci and staphylococci but not to nonhemolytic streptococci, in other words properties similar to those of serums of febrile patients as reported by Tillet and Abernethy. Such observations on exudates, therefore, do not necessarily have a bearing on the question of the etiology of rheumatic fever.

The observation that agglutination tests need bear no relationship to cutaneous tests of skin sensitivity is further borne out by the work of Schultz and Swift [143] on reactions of rabbits to streptococci. Bacterial hypersensitivity to whole streptococci seems to depend more on previously induced focal infection than on circulating antibodies.

Skin Tests and Throat Cultures. In the face of contradictory and varying evidence regarding the specificity, or lack of it, of organisms isolated in blood cultures and the agglutinating properties of the serums of affected patients, many have adopted the allergic theory as an omnibus, believing it helps to explain such conflicting findings. Until recently the idea was dominant that the tissues were allergic first to viridans alone, next to many strains of viridans and indifferent streptococci, and possibly also to nucleoprotein of some staphylococci. The hemolytic streptococcus is now regarded as the chief, if not the sole, offender. Coburn believes that rheumatic fever represents an allergic reaction in individuals sensitive to the nucleoprotein of hemolytic streptococci present in "epidemic" sore throats. In his cases, blood cultures were essentially negative although several hundred cultures were made and 21 different mediums used. As a sequel to his monograph (1931) he has published with Pauli [144, 145, 146] further studies on the relationship of throat infections with hemolytic streptococci to initial and subsequent attacks of rheumatic fever. They feel that certain climates are more favorable to streptococcic infections of the upper respiratory tract. In the tropics, where hemolytic streptococci are unusual in throat flora, scarlet fever is unknown and rheumatic fever is rare. In New York City, however, following epidemics of hemolytic streptococcal pharyngitis, the incidence of rheumatic fever rises precipitously, but during seasons when such throat infections are rare, acute rheumatic fever is unusual. The incidence of rheumatic fever, they insist, bears a striking relationship to geographic and seasonal distribution of hemolytic streptococci. Poverty and unhygienic conditions favor

activity of hemolytic streptococcal throat infections and rheumatic fever, and children of the wealthy rarely have such germs in the throat. Certain patients with rheumatic fever were transplanted to the tropics; while there, hemolytic streptococci previously present were not found in throat cultures. As long as they remained in the tropics the disease remained quiescent. The patient with rheumatic fever who escapes respiratory disease in the North or in the South remains free of rheumatic symptoms.

The chain of events leading to an attack they conceive to be as follows: the appearance of hemolytic streptococci in the throat one to five weeks before the onset of the acute attack, an active throat infection, tonsillitis or nasopharyngitis, followed by about a 10 day quiescent period, then the attack. Details are given concerning immunologic reactions, agglutination, complement fixation and precipitin tests, and antistreptolysins. They suspect that an attack of rheumatic fever may represent the immunity mechanism of certain individuals for handling products of hemolytic streptococci, and that it may begin when the immune response is at its height. At the onset of each attack a rise in antistreptolysin titer of a patient's serum occurs. Hemolytic streptococci isolated were not of a single type but fell into six antigenic groups, the majority being strong toxin producers. About 70 per cent of the toxins were neutralized by a monovalent streptococcal antiserum. Coburn and Pauli concluded that the specificity of the rheumatic response depends not entirely on the character of the parasitic germs but is related to some individual mechanism of the rheumatic patient.

The studies of Collis [147, 148] and his colleagues, Sheldon, Bradley and Coombs,[149, 150] apparently confirm Coburn's findings and conclusions. They believe that the silent or incubation period after the throat infection lasts 7 to 24 days, that hemolytic streptococci can be isolated during the throat infection but tend to disappear rapidly toward the end of the quiescent period, and that they often cannot be found when the rheumatism appears. This explains the failure of many to find a causal organism in the later stages. Blood cultures were repeatedly negative in all stages of the disease. Throat cultures of patients in a rheumatic fever ward were studied throughout several epidemics of sore throat. Relapses in cases of rheumatic fever occurred only after infections with hemolytic streptococci and not following throat infections of other varieties. Skin tests were performed with a hemolytic streptococcal endotoxin and with Dick's streptococcal exotoxin. They gave fewer positive Dick reactions than do normals, but whereas only 20 per cent of controls reacted to the endotoxin, all of the rheumatic fever patients had positive reactions. Rheumatic fever is therefore a contagious disease to those sensitive to hemolytic streptococci, although not contagious in the ordinary sense as more than one factor is responsible for its development. The streptococcal throat infection is no doubt contagious in the epidemic sense, but is followed only by rheumatic fever in the patient who is probably allergic.

Keefer, Myers and Oppel [140] agree that patients with rheumatic fever or

with atrophic arthritis seem to be allergic to the nucleoprotein of hemolytic streptococci; 77 per cent of 40 patients with rheumatic fever and 70 per cent of 20 patients with atrophic arthritis had positive skin reactions thereto as compared with 44 per cent of 207 controls. There was no relation between positive skin tests and agglutination tests. Although such patients are skin sensitive and allergic to such streptococci, the exact relationship between such streptococci and rheumatic fever or atrophic arthritis is not proved, and such streptococci are not necessarily the cause of the diseases.

Culturing throats and making skin tests to hemolytic and green streptococci in cases of rheumatic fever and in a control group, Graham and Thomson,[151] and Gibson, Thomson and Stewart [152] found that there were no essential differences between either group in skin reactions, in the presence or absence of hemolytic streptococci in sore throats, or in the relation between skin reactions and throat cultures; nor did there seem to be a relation between these factors and the patients' clinical condition. They concluded that the allergic skin reaction may be the result of previous infection with hemolytic streptococci, that the intradermal test could not be considered of diagnostic or prognostic value in cases of rheumatic fever, and that while rheumatic fever is probably due to some infective agent that agent has not yet been defined, although its entry may be facilitated by infection with hemolytic streptococci.

Antihemolysins. A method of determining the presence of an infection by hemolytic streptococci without a bacteriologic examination has been described [153]; it is a titration for antistreptolysins in serum. Streptococcal hemolysins are species (group) specific, but not type (strain) specific. To investigate the supposed relation between rheumatic fever and infection by hemolytic streptococci, Todd titrated the serums of patients with rheumatic fever for antihemolysins. Rheumatic patients whose symptoms were quiescent usually had a low antihemolysin titer. Patients with symptoms of active rheumatic disease had a high titer. The titer of individual patients rises during an attack of acute rheumatic fever, falls during a period of quiescence, and rises again with recrudescence of rheumatic symptoms. However, variations in the intensity of rheumatic disease are not necessarily accompanied by corresponding variations in antihemolysin titer. Patients suffering from infections other than rheumatic fever, apparently due to hemolytic streptococci, also show increases in the titer of their serum, but such increases are not present in normal persons or persons with diseases not associated with hemolytic streptococci. Injections of typhoid vaccine do not cause an increase of antihemolysins. Todd concluded that such studies supply further evidence that rheumatic fever is preceded by a hemolytic streptococcal infection but that they do not support the allergic theory or that of direct intoxication.

Precipitin Reactions. Coburn and Pauli noted that, at the appearance of the rheumatic attack, individuals develop precipitins to protein fractions of hemolytic streptococci. These precipitins are not entirely specific since

there is some cross reaction with antigens of chemically related organisms. Schlesinger and Signy [154] also found streptococcic precipitins in the blood of rheumatic patients, but none, or very few, in controls. Their formation is delayed for about 10 to 21 days from the onset of nasopharyngeal infection. Their appearance generally foreshadowed a minor or major relapse of acute rheumatic fever. The peak of precipitin formation coincides roughly with the onset of the relapse. Such formation is but one of manifold reactions that take place in the patients' defense mechanism during the silent period. It is suggested that if the throat infection does not pass unnoticed, prophylactic measures, such as concentrated aspirin therapy, may prevent or minimize the impending relapse. Such medicine seems to delay the formation of precipitins.

Incidence of Other Clinical Evidences of Allergy. According to McLean [155] and Irvine-Jones,[99] the incidence of so-called allergic manifestations (eczema, urticaria, asthma, and hay fever) is no greater in rheumatic than in nonrheumatic children. McLean furthermore found no difference in incidence or severity of upper respiratory tract infections.

Experimental Arthritis. Adherents of the allergic theory may gain support from the work of Magrassi.[156] Intravenous injections of arthrotropic streptococci in rabbits produced septic polyarthritis with destructive changes in joints and no articular or cardiac similarity to rheumatic fever. Intravenous injections into rabbits of serum of patients with rheumatic fever did not produce the histopathologic picture of rheumatic fever, but its intra-articular injection produced nodular proliferations and areas of hyaline-fibrinoid degeneration, none of which were produced by similar injections of serum from febrile patients without rheumatic fever. Arthrotropic strains of living streptococci were injected subcutaneously or intra-articularly. Although local nodular lesions were seen, the development of such systemic lesions did not occur for from 8 to 25 days. Thereafter, the intravenous injection of the same strain of heat-killed streptococci markedly accentuated the production of systemic and diffuse lesions corresponding to those in rheumatic fever of man.

Summarizing data on the infectious theory leads to the obvious conclusion that our knowledge of the bacteriology and immunology of rheumatic fever is still inadequate; that the cause of the disease, which is not yet established, must await much further investigation. Differences of opinion, which now seem insurmountable, may disappear when more data are at hand, particularly regarding the extent to which transmutation of organisms may occur. Rosenow, for example, has long contended that one should not depend on bacterial grouping of streptococci on the basis of hemolysis, and that under changing environment a green streptococcus will readily assume properties of a hemolytic or indifferent type. He feels that, regardless of its hemolysing properties at the moment, the streptococcus probably responsible for each of the diseases, rheumatic fever and atrophic arthritis, is antigenically—serologically—or toxin-specific, acting both through endo-

toxins and exotoxins, especially the former. In little of the work here reviewed have investigators been convinced even of group-specificity, much less of strain-specificity. While they have "generally" found this or that germ, or this or that immune reaction, sufficient cross infection has been found to make it difficult to place them categorically in just one bracket of the schema in table 2.

Other Ideas on Etiology; the Rat-Flea Hypothesis. The theory was recently advanced by Clarke [157] that rheumatic fever is not due to streptococci, but to some protozoön or spirochete carried by the rat-flea (*Ceratophyllus fasciatus*). It is noted that rheumatic fever does not occur in the tropics, or particularly in the Malay states where the climate is inimical to rat-flea. Seasonal and geographic data were presented to strengthen the relationship. Clarke has presented statistics of others to show that, contrary to Coburn's[102] report, hemolytic streptococci can be found in the tropics. It is suggested, however, that climatic conditions there do not favor complete maturation. Studying the incidence of various hemolytic streptococci in the tropics, he noted the fact that streptococci supposed to be the cause of scarlet fever are present in the Malay Archipelago, but the disease does not occur there. If hemolytic streptococci, considered causative of scarlet and rheumatic fever, are found in the tropics but their respective diseases are not, the difference in incidence of the disease in the tropics and elsewhere probably is not due to a difference of bacteria but lies in an agent, such as insect carriers, which can live in one climate and not in another. An infection by hemolytic streptococci may be an excitor of rheumatic fever, but its real cause is an as yet unrecognized organism (lying between bacteria and protozoa), possibly borne by the rat-flea.

Endocrine Theory. Stressing the importance of underlying rheumatic diathesis and criticizing the infectious theory for its inadequacies, Llewellyn [158, 159] has stated his belief that the primary morbid process in acute rheumatism and chorea is one of endocrine-autonomic imbalance, involving especially the sympathetic divisions with their correlated endocrines, the thyroid and suprarenals (sympathetic) and the parathyroids (parasympathetic). Transient phases of thyro-adrenal toxicosis, affecting the cardio-respiratory or vasomotor system, are responsible for transitory cardiac arrhythmias which are a part of the clinical syndrome of acute rheumatism and chorea. If such a toxicosis is prolonged, as in recurring attacks of acute rheumatism or chorea, endocarditis and myocarditis result. Jones [160] discussed Llewellyn's [161, 162] ideas further, and advocated ultra-violet irradiation in the prodromal stages of atrophic arthritis and for the prevention and treatment of rheumatic carditis on the assumption that ultra-violet light is required for the mobilization of tyrosine and cystine from the epidermis via lymph channels into blood. This mobilization is held to be necessary for the production of the hormones thyroxin, epinephrine, and insulin. It is further stated that if ultra-violet irradiation alone can mobilize tyrosine, it would go far to explain why rheumatism is most prevalent in the smoke-ridden areas

where there is an inadequacy of sunshine. Dally [163] also believes that the rheumatic diathesis is in reality an error of metabolism, which is "internally interwoven with hormonic disequilibrium, chiefly in the direction of imbalance of the sympathetic division of the autonomic endocrine system." Studies on acid-base balance, phosphate-sulphate excretion in urine, and calcium excretion in urine and feces are mentioned to illustrate the clinical changes considered characteristic of the diathesis. Dally [164] stated that all children with murmurs or cardiac enlargement had a decreased alkaline reserve in the blood, and that their urine deviated from the acid-base balance in the direction of increased acidity. Errors of purin and mineral metabolism were also suspected. The hemolytic streptococcus is considered provocative of rheumatic fever only among persons who have such an altered metabolism.

Treatment, Salicylates. It has been claimed that salicylates in adequate doses reduce fever, relieve articular pain, shorten both the acute process and the hospital stay necessary, and help to prevent cardiac complications. As to the analgesic and antipyretic values of salicylates there is almost complete agreement, but many do not agree as to their other virtues.

It has been stated that there is no rationale for the administration of salicylates other than by mouth. Brooks [165] felt that the most constantly effective avenue of administration is by rectum, whereby doses of 120 to 180 grains of sodium salicylate, in from two to four ounces of warm water or milk, are given one to three times a day through catheter and syringe (introduced six to eight inches up from the anus). Brooks considers salicylates of "tremendous value," giving more relief from agonizing pain "than all other measures put together." However, the administration of sodium salicylate does not prevent complications, shorten the course, or modify the prognosis. It has nothing to do, Brooks felt, with the production of the severe anemia which often accompanies rheumatic fever, nor does it have any effect on anemia once it is present. It has few unfavorable effects and does not disturb the heart. When given properly, it is entirely without danger.

Master and Romanof [166] studied the course of the disease in 30 cases of rheumatic fever in which patients were not given salicylates and in 33 cases in each of which they had 8 to 12 gm. (120 to 180 grains) of salicylates daily. One hundred per cent in each group developed heart involvement on the basis of electrocardiographic alterations whose qualitative and quantitative changes were essentially the same. The course of the disease and the appearance of pericarditis and other complications were about equal in both groups. There was no material shortening of the stay in the hospital. Master and Romanof concluded that whereas at present salicylates are most efficient antipyretics and analgesics, they do not prevent cardiac complications or have a curative effect.

A somewhat similar study was made by Perry [167] who gave 10 grains of acetylsalicylic acid, three times daily for 12 months, to each of 41 children

who were suffering from rheumatic heart disease. A control group was untreated. In the treated group relapses of a rheumatic nature (chorea, arthritis, or carditis) occurred in 12 per cent of cases, and in the control group in 18 per cent the difference being due, Perry felt, to factors other than the drug. No significant changes were noted in cardiac signs or general health, and little evidence was obtained that the prolonged administration of salicylates prevents relapses.

Poynton [116] was disappointed in salicylate therapy for rheumatic heart disease, and believes that it may actually do harm. He prefers neocinchophen. According to Foxe [168] the toxic effect is minimal when salicylates are combined with sodium bicarbonate or magnesium oxide. Salicylates are effective in smaller doses with magnesium oxide. He felt that 90 grains of sodium salicylate daily with 60 grains of magnesium oxide are the equivalent of 150 grains each of sodium salicylate and sodium bicarbonate combined.

Other Drugs. Magnesium also "potentiates" cinchophen, according to Tolstoi and Corke [169] who combined magnesium oxide and magnesium cinchophen into a preparation "magnephen" for the treatment of seven patients with rheumatic fever. Because of "magnesium potentiation," the therapeutic doses are smaller and nontoxic. Doses as large as 2,130 grains (142 gm.) over 26 days were well tolerated. The preparation relieves pain and reduces fever but has no influence on the rheumatic virus, as is evidenced by a persisting leukocytosis and increased sedimentation time.

The sodium salt of phenyl-ethyl hydantoin (nirvanol) was recently introduced in Germany and England for the treatment of chorea, acute and subacute rheumatism. The type of reaction it produces (drowsiness, stupor, fever, rash, eosinophilia, leukopenia), the results of its administration, its mode of action, and its dangers, have been reviewed (Poynton and Schlesinger, 1931, and Council on Pharmacy and Chemistry,[170] 1932). Schlesinger [170a] has reported its presumably beneficial effects in the case of a seven year old boy who suffered for two years with chorea, rheumatic fever, and carditis. The drug stops chorea, reduces fever, and causes rheumatic nodules to disappear in some cases. In the discussion of this report the use of nirvanol was sharply criticized by Slot,[171] Collis,[148] and Findlay,[172] who not only consider it useless but sometimes quite dangerous. Schlesinger insisted that it is only dangerous if given in the wrong type of case, such as in chorea or rheumatic fever where mental symptoms are a dominant factor. No reports of its use in rheumatic fever have appeared in American literature although it has been used for chorea. Satisfactory results in chorea were obtained in 15 cases by Murray-Lyon,[173] in 72 cases by Dennett and Wetchler,[174] in 16 cases by Whitaker [175] and in 21 additional cases by Dennett.[176] No relief was noted in three cases by Jones and Jacobs,[177] who observed a dangerous pulmonary hemorrhage in one, or in six cases by Weinfeld and Cohen.[178] Facial edema was noted in one case (Murray-Lyon). Nirvanol has not been accepted by the Council on Pharmacy and Chemistry [170] because, although a fairly large percentage of patients with

chorea are relieved thereby, side actions are disagreeable, sometimes dangerous, and the treatment is too severe to justify its use except in very resistant cases.

Tonsillectomy. There are still considerable differences of opinion as to the value of tonsillectomy in the treatment and prophylaxis of rheumatic fever and carditis. Collis, Bradley, and Coombs [149] feel that tonsillectomy in the prevention of rheumatism is a lost cause. Many of McLean's patients made little or no improvement after the tonsils and adenoids were removed, but in those cases where the results of tonsillectomy were disappointing, an infection in the sinuses was almost invariably found later.

Considering the fact that removal of foci, particularly tonsillectomy, has been carried out strenuously in the past 25 years, Davis [94] agreed with others that removal of foci has not influenced the clinical course or spread of rheumatic fever. Of 185 patients with rheumatic fever, 88 per cent had their tonsils removed but 77 per cent had recurrences within one to eleven years (Ingerman and Wilson, 1924). Of 97 patients who did not have their tonsils removed, 80 per cent had recurrences. Davis recounts Kaiser's statistics (1930). Rheumatism occurred among 8 per cent of 20,000 school children who had had their tonsils out at least five years previously. It occurred among 10 per cent of 28,000 children who still had their tonsils. Recurrences of rheumatic fever, however, were decidedly less common and the incidence of carditis and chorea seemed less in the former group.

When rheumatic heart disease is present in children, tonsillectomy is a serious step, according to Poynton, and should be done preferably in a period of quiescence. Herrick [179] also believes that tonsillectomy during an acute attack of rheumatic fever may be dangerous; after tonsillectomy, the blood culture may become positive and the clinical picture may change for the worse. In general, it seems best to wait until the acute manifestations have subsided. However, in the prolonged and recurrent cases, Herrick believes a different attitude may be taken with advantage.

Tonsillectomy during an acute attack of rheumatic fever is considered by Robey [180] to be not only essentially harmless, but often of distinct value, and in his experience has sometimes proved an efficient means of stopping an attack when ordinary measures failed. Cases are described in which fever and arthritis persisted beyond the usual period in spite of intensive medical treatment and in which within a few days after tonsillectomy symptoms disappeared. In two or three cases only temporary recrudescences of joint symptoms followed tonsillectomy during fever, but they promptly disappeared. Tonsillectomy in the presence of fever and inflamed joints is no more dangerous than tonsillectomy in the interval between attacks. It should not be performed while acute tonsillitis is present, but this question seldom arises since acute rheumatic fever is usually a sequel, not a concomitant, of tonsillitis. Only complete enucleation is successful; radium and roentgen-ray treatments to tonsils are inadequate.

Stroud and his colleagues [125] concluded that though there is no positive

proof that routine tonsillectomy prevents primary or subsequent attacks of rheumatic fever, such a procedure, if combined with careful examination of the sinuses for infection, is still justified. Cecil [110] also advocated giving the patient the benefit of the doubt, and he advises tonsillectomy, as also does Miller.[181]

Although Robey was of the opinion that tonsillectomy during the acute attack is not essentially dangerous, and in individual cases may be of benefit in shortening attacks, he, with Finland and Heimann,[182] believed that a study of groups indicates that tonsillectomy has little influence on frequency of recurrences. Six hundred and fifty-four consecutive patients were admitted to a hospital on account of "acute migratory polyarthritis." Many had undergone tonsillectomy previously; in some cases the tonsils were removed while the patients were in the hospital. Those whose tonsils had been removed previously had on the whole a similar course in the hospital to those operated on after admission. The latter, however, had a slightly longer period of joint symptoms and of hospitalization than those whose tonsils were left untouched.

Vaccines, Antigens, Serums. Their opinions on the value of the newer bacterial products in the immunization and desensitization treatment of rheumatic fever have not been re-stated during the past two years by the originators. Whitten [183] has reported on the use of Small's *Streptococcus cardio-arthritidis* (S.C.A.) bovine serum intramuscularly, and S.C.A. antigen given later subcutaneously. In the author's limited experience acute rheumatic fever responded promptly to the antiserum. In every case (number not stated) the injection of 20 c.c. of antiserum was followed by disappearance of fever and arthritis within 24 hours, the patient to all outward appearances being cured. Three of the author's local colleagues reported similar results. Recalling reports of failure by others, Whitten believes Small's products are now in a greater state of perfection. Five patients with chronic rheumatic endocarditis were definitely benefited. Each time antiserum and antigen were given, signs and symptoms of cardiac decompensation diminished. Small (1927) and others originally had difficulty in planning dosages which would avoid reactions. The author's plan is detailed.

Collis and Sheldon [150] treated 47 children who had rheumatic fever with intravenous injections of a vaccine of heat-killed hemolytic streptococci. In some cases the treatment was discontinued for various reasons, such as the development of an acute sore throat or the appearance of a pericardial rub. The treatment had no effect on vague pains in limbs loosely termed "subacute rheumatism." In acute cases, when the treatment was well borne, "encouraging clinical improvement" was noted: skin tests became negative in 64 per cent of cases and agglutinins appeared at times in the blood serum. Streptococcal vaccine given intravenously to 10 patients with rheumatic cardiovascular disease, by Stroud, Bromer and Gallagher,[184] did not diminish the incidence of acute exacerbations of rheumatic fever the following season.

Results were comparable to those observed for 10 untreated controls and for 10 who were given typhoid vaccine intravenously. Three or four in each group obtained some immediate relief, however.

Wilson and Swift (1931) observed that 45 per cent of children with rheumatic fever who were treated with hemolytic streptococcal vaccine remained free of rheumatic arthritis for from 16 to 24 months, compared to 18 per cent for those not so treated. The result may have been merely coincidental or from immunization or desensitization. Further observations in this group of 166 cases and in an additional 141 cases have been made by Wilson, Josephi, and Lang.[185] Vaccine was stopped in some cases and continued in others, using variously typhoid bacilli, *Streptococcus viridans*, or hemolytic streptococci intravenously. The results indicated that intravenous vaccination with various antigens in the doses used did not influence the incidence of recurrence of rheumatic activity, and that the temporary diminished incidence of recurrence previously noted after intravenous treatment was probably unrelated to the treatment.

Additional Treatment. A review of six years' experience with the treatment by roentgen irradiation of 32 patients with rheumatic heart disease is given by Levy and Golden.[186] Seven of the 32 have since died. In eight cases there was no, or doubtful, improvement. Seventeen patients showed improvement; there was relief of paroxysmal cardiac pain with some, and improvement in the electrocardiogram with a number of them. (The report cannot be evaluated as no control series was studied.—Ed.)

Whether a woman with rheumatic fever should subsequently be permitted to marry and have children is discussed by Meakins,[109] who was of the opinion that the guiding principle should be this: if a number of years without recurrence have elapsed since the original infection, if cardiac signs have been stationary, if there is no enlargement of the liver or engorgement of the lungs, and if the woman is able to do what an ordinary person can do, she should be permitted to marry but her husband should be told of her condition. Usually, patients take these matters into their own hands, and if they do not feel well they will not have children. A woman with mitral stenosis, without incapacity, has been known to have 12 children or more without trouble. If there are signs of failing circulation, the patient should not marry; she may go through one or more pregnancies quite well, but difficulties may develop later.

BIBLIOGRAPHY

1. PEMBERTON, R.: The work of the American Committee for the Control of Rheumatism: the present status of arthritis, Med. Jr. and Rec., 1933, cxxxviii, 359–363.
2. Revue du rheumatisme, Paris, 23, Rue du Cherche-Midi.
3. Acta Rheumatologica. Official Journal of the Ligue Internationale Contre Le Rheumatisme. Headquarters, Holland, Amsterdam, Keizersgracht 489.
4. Conference scientifique internationale du rheumatisme chronique; progressif, géneralise; Aix-les-Baines, rapports, 1934. Imprimeries Reunies de Chambery, 3 Rue Lamartine.
5. Revue de medicine (Numero consacré aux rheumatismes). Felix Alcan, 108 Boulevard Saint-Germain, Paris, 1933, 1, 279–364. *Ibid.*, 1934, li, 245–295.

6. Van Breemen: Review of rheumatism and arthritis. *In:* Internat. Med. Annual, 1932, William Wood and Company, New York.
7. Rheuma Jahrbuch, 1930–1931. Berlin, Charlottenburg 9, Leo Alterthum, 196 pp.
8. Rheumaprobleme. Leipzig, Georg Thieme, 1934, 95 pp.
9. Fox, R. F.: Social and industrial aspects of rheumatism, Jr. State Med., 1933, xli, 263–288.
10. Glover, J. A., and Newman, G.: Ministry of health; the incidence of rheumatic diseases. Reports on public health and medical subjects, London, no. 23, 1924.
11. Connan, D. M.: Social burden of rheumatic diseases, Jr. State Med., 1932, xl, 249–254.
12. Fox, R. F.: Rise of conception of rheumatism as social problem, Jr. State Med., 1932, xl, 209–225.
13. Boyd, J.: Rheumatism as a factor in employment, Jr. State Med., 1933, xli, 295–300.
14. Buckley, C. W.: The economics of rheumatism, Jr. State Med., 1933, xli, 282–294.
15. Copeman, W. S. C.: Control of industrial rheumatism, Lancet, 1932, i, 967–970.
16. Copeman, W. S. C.: Control of industrial rheumatism, Jr. State Med., 1933, xli, 476–481.
17. Buckley, C. W.: Rheumatism costs the country $100,000,000 a year, Jr. Am. Med. Assoc., 1932, xcix, 1701.
18. Dublin, L. I.: The incidence of rheumatic disease. *In:* Wyatt, B. L.: Chronic and rheumatoid affections, 1930, William Wood and Company, New York, pp. 1–19. *Also in:* Wyatt, B. L.: Chronic arthritis and fibrositis; diagnosis and treatment, 1933, William Wood and Company, New York, 201 pp.
19. Osgood, R. B.: Human and economic problem of chronic arthritis, New England Med. Jr., 1932, ccvi, 1–6.
20. Bigelow, G. H., and Lombard, H. L.: Cancer and other chronic diseases in Massachusetts, 1933, Houghton Mifflin Co., New York, 355 pp.
21. Matz, P. B.: Clinical and economic features of arthritis in ex-members of military service, New England Jr. Med., 1933, ccix, 547, 597, 639.
22. Kahlmeter, G. (Cited by Fox [9]): Modern physiotherapeutic measures, Proc. Roy. Soc. Med., 1932, xxv, 1117–1129.
23. Coates, V., and Delicati, L.: The correlation between certain rheumatic disorders and occupation, Acta rheumatologica, 1932, iv, 28–32.
24. Holt: Cited by Buckley.[14]
25. Danischevsky: Cited by Fox.[9, 12]
26. Thomson, J. E. M.: Industrial accidents and chronic arthritis, Nebraska Med. Jr., 1932, xvii, 324–327.
27. Fischer: Cited by Fox.[9, 12]
28. Buckley, C. W.: Control and treatment of chronic arthritis, Brit. Med. Jr., 1932, i, 140–142.
29. Kahlmeter, G.: Du rôle joué en suède par le rheumatisme articulaire chronique comme cause d'incapacité permanente de travail dans les divers groupes professionels, Acta rheumatologica, 1932, iv, 34–36.
30. Fischer: Cited by Fox.[9]
31. Freund: Cited by Fox.[9, 12]
32. Edstrom: Cited by Fox.[9, 12]
33. Warner, E. C.: Relation of soil and climate to rheumatic disease, Jr. State Med., 1933, xli, 621–629.
34. Thiem: Cited by Fox.[9, 12]
35. Weisz: Cited by Fox.[9, 12]
36. Key, J. A.: Experimental arthritis, chronic and atrophic, Med. Jr. and Rec., 1933, cxxxviii, 369–372.
37. Doub, H. P.: Relation of trauma to arthritis, Am. Jr. Roentgenol., 1933, xxx, 26–33.
38. Cotton, F. J.: Traumatic arthritis, New England Jr. Med., 1933, ccviii, 829–831.

39. SANTOS, J. V.: Changes which articular cartilage of hip joint may undergo, Surg., Gynec. and Obst., 1932, liv, 650–662.
40. RAY, M. B.: Prevention and treatment of industrial rheumatism, Jr. State Med., 1932, xl, 255–273.
41. CARP, L.: Tennis elbow (epicondylitis) caused by radiohumeral bursitis; anatomic, clinical, roentgenologic and pathologic aspects, with suggestions as to treatment, Arch. Surg., 1932, xxiv, 905–922.
42. NAIRN, S. J. G.: Rheumatism in London busmen, Brit. Jr. Phys. Med., 1932, vi, 241–245.
43. HOETS, J.: Drivers' thigh, Med. Jr. Australia, 1932, i, 265.
44. TITUS, N. E.: Traumatic synovitis, Arch. Phys. Therap., 1933, xiv, 285–286.
45. JOHNSON, M. A., JR.: Hemarthrosis, Va. Med. Month., 1932, lix, 457–464.
46. DIAMOND, J. C.: Three cases of patellar bursitis treated by injection of tincture of metaphen with apparent cure, Can. Med. Assoc. Jr., 1933, xxviii, 419–420.
47. FRASER, I.: A very large bursa; case, Lancet, 1932, i, 290–291.
48. KING, E. S. J.: The pathology of ganglion, Aust. and New Zealand Jr. Surg., 1932, i, 367–381.
49. KIDNER, C. F.: Industrial backs, Jr. Mich. State Med. Soc., 1933, xxxii, 419–428.
50. NELIGAN, A. R.: Organization of treatment for industrial rheumatism, Jr. State Med., 1932, xl, 274–299.
51. CALDWELL, G. A.: Acute suppurative conditions of the hip, Jr. Am. Med. Assoc., 1932, xcviii, 37–40.
52. BISGARD, J. D.: Relation of pyogenic arthritis to osteomyelitis, Surg., Gynec. and Obst., 1932, lv, 74–80.
53. SEVIER, C. E.: Surgical forms of non-tuberculous joint disease, Colorado Med., 1932, xxix, 251–253.
54. FOSTER, J. B.: Acute purulent arthritis of the hip, Texas State Jr. Med., 1932, xxviii, 476–478.
55. BEEKMAN and WILENSKY: Cited by Bisgard.[52]
56. LEES, D.: Gonococcal arthritis with observations based on a series of 388 cases, Brit. Jr. Vener. Dis., 1932, viii, 8–79, 192.
57. MCCAHEY, J. F.: History of gonorrheal arthritis, Brit. Jr. Vener. Dis., 1933, ix, 194–201.
58. MCCAHEY, J. F.: Important factors in the onset and course of arthritis complicating gonorrhea in the adult male, Urol. and Cutan. Rev., 1933, xxxvii, 217–222.
59. DELACROIX, A.: Traitement des arthrites blennorragiques par les eaux thermo-minérales radio-actives, Arch. Med. Hydrol., 1932, x, 82–83.
60. GINSBERG, S.: Roentgenographic findings in acute gonococcal synovitis of the knee treated by pneumarthrosis: report of two cases with a plea for early motion, Jr. Bone and Joint Surg., 1933, xv, 615–621.
61. GREEN, F.: Complement fixation in gonorrheal arthritis, Can. Med. Assoc. Jr., 1933, xxviii, 289–292.
62. OPPEL, T. W., MYERS, W. F., and KEEFER, C. S.: Sedimentation rate of the red blood cells in various types of arthritis, Jr. Clin. Invest., 1933, xii, 291–296.
63. NEELY, J. W.: Arthrotomy for neisserian arthritis, Tri-State Med. Jr., 1932, iv, 940–944.
64. LEBRETON, P.: Results of irrigation and closure in selected cases of non-pyogenic arthritis, Jr. Florida Med. Assoc., 1932, xviii, 409–412.
65. THOMSON, J. E. M.: Clinical and experimental observations with regard to injection of certain agents (Pregl's solution) into arthritic joints, Jr. Bone and Joint Surg., 1933, xv, 483–490.
66. CARPENTER, C. M., BOAK, R. A., MUCCI, L. A., and WARREN, S. L.: Studies on physiological effects of fever temperatures; thermal death time of neisseria gonorrheae in vitro with special reference to fever temperatures, Jr. Lab. and Clin. Med., 1933, xviii, 981–990.

67. Bishop, F. W., Horton, C. B., and Warren, S. L.: A clinical study of artificial hyperthermia induced by high frequency currents, Am. Jr. Med. Sci., 1932, clxxxiv, 515–533.
68. Tenney, C. F.: Artificial fever produced by short wave radio and its therapeutic application, Ann. Int. Med., 1932, vi, 457–468.
69. Warren, S. L., and Wilson, K. M.: Treatment of gonococcal infections by artificial (general) hyperthermia; preliminary report, Am. Jr. Obst. and Gynec., 1932, xxiv, 592–598.
70. Berris, J. M.: The treatment of arthritis by artificial fever; preliminary report of 20 cases, Jr. Mich. State Med. Soc., 1933, xxxii, 355–358.
71. Simpson, W. M., Kislig, F. K., and Sittler, E. C.: Ultrahigh frequency pyretotherapy of neurosyphilis: a preliminary report, Ann. Int. Med., 1933, vii, 64–75.
72. Atsatt, R. F., and Patterson, L. E.: The use of electropyrexia in gonorrheal arthritis, Physiotherapy Rev., 1933, xiii, 144–146.
73. Phemister, D. B., and Hatcher, C. H.: Correlation of pathological and roentgenological findings in the diagnosis of tuberculous arthritis, Am. Jr. Roentgenol., 1933, xxix, 736–752.
74. Pomeranz, M. M.: Roentgen diagnosis of bone and joint tuberculosis, Am. Jr. Roentgenol., 1933, xxix, 753–762.
75. Darling, H. C. R.: Senile tuberculous arthritis, Med. Jr. Australia, 1932, ii, 51–52.
76. Cooperman, M. B.: Guinea-pig test and biopsy in early diagnosis of articular tuberculosis, Med. Jr. and Rec., 1932, cxxxv, 420–422.
77. Ghormley, R. K., and Brav, E. A.: Resected knee joints, Arch. Surg., 1933, xxvi, 465–484.
78. Smith, A. D.: Monarticular arthritis simulating tuberculosis; clinical and pathologic study of 24 cases, Arch. Surg., 1932, xxv, 54–64.
79. Ory, D.: Du rôle de la tuberculose dans les rheumatismes, Acta rheumatologica, 1932, iv, 8–16.
80. Cooperman, M. B.: Chronic tuberculous polyarthritis, Ann. Surg., 1932, xcvi, 1065–1077.
81. Kling, D. H.: Syphilitic arthritis with effusion, Am. Jr. Med. Sci., 1932, clxxxiii, 538–549.
82. O'Reilly, A.: Syphilis of the osseous system, Missouri State Med. Assoc. Jr., 1932, xxix, 577–580.
83. Keefer, C. S., and Myers, W. K.: The differential diagnosis of acute arthritis, Med. Clin. N. Am., 1933, xvi, 929–942.
84. Morrissey, M. J., and Reynolds, H. S.: Syphilitic bursopathy (luetic bursopathy of Verneuil), Jr. Am. Med. Assoc., 1933, c, 1229–1230.
85. Hunsaker, C. A.: Charcot's disease of the hip: report of case, Med. Bull. Vet. Admin., 1932, viii, 155–156.
86. van Nostrand, F. H., and Baillie, W.: Charcot's joint of lumber vertebrae, Can. Med. Assoc. Jr., 1932, xxvii, 644–645.
87. Warfield, C. H.: Charcot's disease of elbow joint, Am. Jr. Roentgenol., 1933, xxix, 530–532.
88. Keller, H.: Arthritis: some practical hints, Internat. Jr. Med. and Surg., 1932, xlv, 258–266.
89. Woldenberg, S. C.: Arthritis of spine, Med. Bull. Vet. Admin., 1932, viii, 113–118.
90. Kulowski, J., and Vinke, T. H.: Undulant (Malta) fever spondylitis: report of a case due to *Brucella melitensis*, bovine variety, surgically treated, Jr. Am. Med. Assoc., 1932, xcix, 1656–1659.
91. O'Donoghue, A. F.: Septic arthritis in the hip caused by *Brucella melitensis*, Jr. Bone and Joint Surg., 1933, xv, 506–508.
92. Hazard, J. B., and Goodkind, R.: Haverhill fever (erythema arthriticum epidemicum). A case report and bacteriologic study, Jr. Am. Med. Assoc., 1932, xcix, 534–538.

93. GAMMEL, J. A., and MORITZ, A. R.: Experimental monosporosis, Arch. Dermat. and Syph., 1933, xxvii, 100–106.
94. DAVIS, J. S., JR.: Incidence of rheumatic fever in New York City hospitals, Am. Jr. Med. Sci., 1933, clxxxvi, 180–191.
95. CLARKE, J. T.: Cited by Gray, Fendrick and Gowen.[107]
96. PAUL, J. R., and LEDDY, P. A.: The social incidence of rheumatic heart disease, Am. Jr. Med. Sci., 1932, clxxxiv, 597–610.
97. MCLEAN, C. C.: Age incidence and climatic variations in the manifestations of so-called rheumatic fever in white children, Jr. Pediatrics, 1933, ii, 320–330.
98. MCLEAN, C. C.: Early manifestations of rheumatic infections in young children, ANN. INT. MED., 1932, v, 1357–1366.
99. IRVINE-JONES, E.: Acute rheumatism as a familial disease, Am. Jr. Dis. Child., 1933, xlv, 1184–1195.
100. JAMIESON, H. C.: Case of rheumatic fever with familial and hereditary characteristics, Can. Med. Assoc. Jr., 1933, xxviii, 304–305.
101. GRAHAM, H. C.: Rheumaticosis, Jr. Oklahoma Med. Assoc., 1932, xxv, 427–429.
102. COBURN, A. F.: Relationship of the rheumatic process to the development of alterations in tissues, Am. Jr. Dis. Child., 1933, xlv, 933–972. The factor of infection in the rheumatic state, 1931, Williams and Wilkins Company, Baltimore, 288 pp.
103. DALLY, J. F. H.: Problem of rheumatism restated, Internat. Jr. Med. and Surg., 1932, xlv, 441–445.
104. SIGLER, L. H.: Clinical manifestations of rheumatic fever, Internat. Clinics, 1933, iii, 178–185.
105. GRAEF, I., PARENT, S., ZITRON, W., and WYCKOFF, J.: Studies on rheumatic fever. I. Natural course of acute manifestations of rheumatic fever uninfluenced by "specific" therapy, Am. Jr. Med. Sci., 1933, clxxxv, 197–210.
106. BURNETT, C. T.: Rheumatic heart disease: a review, ANN. INT. MED., 1932, v, 1337–1356.
107. GRAY, J. W., FENDRICK, E., and GOWEN, C. H.: Rheumatic fever and rheumatoid arthritis, Texas State Jr. Med., 1932, xxviii, 203–213.
108. GRAY, J. W., FENDRICK, E., and GOWEN, C. H.: Rheumatic fever and rheumatoid arthritis from laboratory point of view, Texas State Jr. Med., 1932, xxviii, 317–327.
109. MEAKINS, J. C.: Rheumatic fever, Med. Clin. N. Am., 1932, xvi, 609–624.
110. CECIL, R. L.: The heart in rheumatic disease, Internat. Jr. Med. and Surg., 1932, xlv, 57–60.
111. CECIL, R. L.: Differential diagnosis of rheumatic fever and rheumatoid arthritis, Lib. Anniv. Vol., 1933, i, 303–312.
112. BROOKS, H., and O'REGAN, C.: Manner of onset in acute rheumatic fever as seen in New York City, ANN. INT. MED., 1932, vi, 717–723.
113. SCHWARZ, H.: Unusual case of acute rheumatic fever in infant, Lib. Anniv. Vol., 1932, iii, 1061–1068.
114. PAYNE, W. W.: Acute rheumatism and sedimentation rate in children, Lancet, 1932, i, 74–75.
115. BACH, F., and HILL, N. G.: Erythrocyte sedimentation rate in rheumatic fever, Lancet, 1932, i, 75–77.
116. POYNTON, F. J.: The prognosis and treatment of rheumatic heart disease in childhood, Practitioner, 1933, cxxx, 638–649.
117. MASTER, A. M., and JAFFE, H.: Rheumatoid (infectious) arthritis and acute rheumatic fever: differential diagnosis, Jr. Am. Med. Assoc., 1932, xcviii, 881–882.
118. MCEWEN, C.: Cytologic studies on rheumatic fever (1) the characteristic cell of the rheumatic granuloma, Jr. Exper. Med., 1932, lv, 745–759.
119. DAWSON, M. H.: Comparative study of subcutaneous nodules in rheumatic fever and rheumatoid arthritis, Jr. Exper. Med., 1933, lvii, 845–858.
120. FRASER, A. D.: Rheumatic lesions in lymph nodes, Lancet, 1933, i, 1117–1119.

121. Coombs, C. F.: Rheumatic fever from clinical standpoint, Clin. Jr., 1933, lxii, 54–56.
122. Sloan, R. M.: Heart in infancy and childhood, West Virginia Med. Jr., 1933, xxix, 226–227.
123. Coombs, C. F.: What proportion of organic disease of the heart is due to rheumatism? Acta rheumatologica, 1932, iv, 22–24.
124. Davis, D., and Weiss, S.: Rheumatic heart disease. II. Incidence and distribution of the age of death, Am. Heart Jr., 1932, viii, 182–189.
125. Stroud, W. D., Goldsmith, M. A., Polk, D. S., and Thorp, F. Q.: Ten years' observation of children with rheumatic heart disease, Jr. Am. Med. Assoc., 1933, ci, 502–507.
126. De La Chapelle, C. E., and Graef, I.: Polyserositis (Pick's syndrome) associated with rheumatic valvular disease without pericarditis, Med. Clin. N. Am., 1933, xvii, 147–163.
127. Gouley, B. A., and Eiman, J.: The pathology of rheumatic pneumonia, Am. Jr. Med. Sci., 1932, clxxxiii, 359–381.
128. Howard, C. P.: The rheumatic lung, Ann. Int. Med., 1933, xvii, 165–171.
129. Myers, W. K., and Ferris, E. B., Jr.: Pleurisy in rheumatic fever; clinical observations, Arch. Int. Med., 1933, lii, 325–337.
130. Shambaugh, P.: Azotemia due to low blood pressure; its occurrence in an unusual case of acute rheumatic fever, Arch. Int. Med., 1932, l, 921–925.
131. Bell, E. T.: Glomerular lesions associated with endocarditis, Am. Jr. Path., 1932, viii, 639–664.
132. Baehr, G., and Schifrin, A.: Rarity of glomerulonephritis in rheumatic fever and its significance, Lib. Anniv. Vol., 1932, i, 125–131.
133. Miller, J. L.: Chronic arthritis. Classification and treatment, Northwest Med., 1933, xxxii, 45–52.
134. Wilson, M. G., and Edmond, H.: Blood cultures in children with rheumatic fever, Am. Jr. Dis. Child., 1933, xlv, 1237–1246.
135. Callow, B. R.: Bacteriologic investigation of the blood in rheumatic fever: presenting evidence of dissociation of micro-organisms recovered from blood cultures, Jr. Infect. Dis., 1933, lii, 279–353.
136. Cooley, L. E.: Blood culture in rheumatic fever, Jr. Infect. Dis., 1932, l, 330–332.
137. Whitaker, W. M.: The bacterium of acute rheumatism: report of fatal case, Jr. Missouri Med. Assoc., 1932, xxix, 134–136.
138. Scudder, S. A.: Septicemia due to higher bacteria; case report (rheumatic heart disease) and bacteriologic findings, Jr. Lab. and Clin. Med., 1932, xviii, 187–188.
139. Clawson, B. J., Wetherby, M., Hilbert, E. H., and Hilleboe, H. E.: Streptococci agglutination in chronic arthritis and acute rheumatic fever, Am. Jr. Med. Sci., 1932, clxxxiv, 758–762.
140. Keefer, C. S., Myers, W. K., and Oppel, T. W.: Streptococcal agglutinins in patients with rheumatoid (atrophic) arthritis and acute rheumatic fever, Jr. Clin. Invest., 1933, xii, 267–277.
141. Tillet, W. S., and Abernethy, T. J.: Serological reactions with hemolytic streptococci in acute bacterial infections, Bull. Johns Hopkins Hosp., 1932, l, 270–286.
142. Hitchcock, C. H., and Swift, H. F.: The agglutinating properties of exudates from patients with rheumatic fever, Jr. Clin. Invest., 1933, xii, 673–681.
143. Schultz, M. P., and Swift, H. F.: Reaction of rabbits to streptococci: comparative sensitizing effect of intracutaneous and intravenous inocula in minute doses, Jr. Exper. Med., 1932, lv, 591–601.
144. Coburn, A. F., and Pauli, R. H.: Studies on relationship of *Streptococcus hemolyticus* to the rheumatic process: Observation on the ecology of the hemolytic streptococcus in relation to the epidemiology of rheumatic fever, Jr. Exper. Med., 1932, lvi, 609–632.
145. Coburn, A. F., and Pauli, R. H.: Studies on the relationship of *Streptococcus hemo-*

lyticus to the rheumatic process. Observations on the biological character of *Streptococcus hemolyticus* associated with rheumatic heart disease, Jr. Exper. Med., 1932, lvi, 633–650.

146. Coburn, A. F., and Pauli, R. H.: Studies on the relationship of *Streptococcus hemolyticus* to the rheumatic process: observations on immunological responses of rheumatic subjects to hemolytic streptococcus, Jr. Exper. Med., 1932, lvi, 651–676.
147. Collis, W. R. F.: Contagious factor in etiology of rheumatic fever, Am. Jr. Dis. Child., 1932, xliv, 485–493.
148. Collis, W. R. F.: Discussion (paper by Schlesinger), Proc. Roy. Soc. Med., 1932, xxv, 717.
149. Collis, W. R. F., Bradley, W. H., and Coombs, C. F.: Discussion on some problems concerning prevention and treatment of acute rheumatic infection, Proc. Roy. Soc. Med., 1932, xxv, 1631–1642.
150. Collis, W. R. F., and Sheldon, W.: Intravenous vaccines of hemolytic streptococci in acute rheumatism of childhood, Lancet, 1932, ii, 1261–1264.
151. Graham, H. J., and Thomson, W. A. R.: Study of the etiology of acute rheumatism with special reference to the relationship of the hemolytic streptococcus to the disease, Trans. Med. Chir. Soc. Edinburgh, 1932–1933, xciii.
152. Gibson, H. J., Thomson, W. A. R., and Stewart, D.: The hemolytic streptococcus as a factor in the causation of acute rheumatism, Arch. Dis. Child., 1933, viii, 57–72.
153. Todd, E. W.: Antihemolytic titres in hemolytic streptococcal infections and their significance in rheumatic fever, Brit. Jr. Exper. Path., 1932, xiii, 248–259.
154. Schlesinger, B., and Signy, A. G.: Precipitin reaction in blood of rheumatic patients following acute throat infections, Quart. Jr. Med., 1933, ii, 255–266.
155. McLean, C. C.: So-called allergic manifestations and the incidence of respiratory infections in rheumatic and in non-rheumatic children, Arch. Pediatrics, 1933, l, 123–129.
156. Magrassi, F.: Experimental infectious rheumatism and streptococcal focal infection, Acta rheumatologica, 1933, v, 2–10.
157. Clarke, J. T.: The nature of the rheumatic poison, Jr. Trop. Med., 1932, xxxv, 55–58.
158. Llewellyn, L. J.: Cardiac fallacy in acute rheumatism, Brit. Jr. Phys. Med., 1932, vi, 208–211.
159. Llewellyn, L. J.: The sebaceous glands in relation to rheumatism in childhood, Internat. Jr. Med. and Surg., 1932, xlv, 395–402.
160. Jones, A. B.: Light in relation to rheumatism, Brit. Jr. Physical Med., 1932, vi, 215–218.
161. Llewellyn, L. J., and Jones, A. B.: New theory of mechanism of ultra-violet irradiation in rheumatic disease, Brit. Jr. Phys. Med., 1932, vi, 181–184.
162. Llewellyn, L. J., and Jones, A. B.: Proximate or basal cause of rheumatism, Med. Jr. and Rec., 1933, cxxxvii, 397–402.
163. Dally, J. F. H.: Problem of rheumatism restated, Internat. Jr. Med. and Surg., 1932, xlv, 441–445.
164. Dally, J. F. H.: Physical methods in prevention of juvenile rheumatism, Brit. Jr. Phys. Med., 1932, vii, 79–81.
165. Brooks, H.: The salicylates in rheumatic fever, Jr. Med. Soc. New Jersey, 1933 xxx, 550–555.
166. Master, A. M., and Romanof, A.: Treatment of rheumatic fever with or without salicylates; clinical and electrocardiographic studies, Jr. Am. Med. Assoc., 1932, xcviii, 1978–1980.
167. Perry, C. B.: The value of salicylates in the prevention of rheumatic relapses, Lancet, 1933, i, 861–862.
168. Foxe, A. N.: The use of sodium salicylate and magnesium in the treatment of rheumatic fever and acute infectious arthritis, West Virginia Med. Jr., 1933, xxix, 212–216.
169. Tolstoi, E., and Corke, D. R.: Treatment of rheumatic fever with magnesium cincho-

phen, magnesium oxide (magnephen) preparation, Jr. Lab. and Clin. Med., 1932, xvii, 450–455.

170. Council on Pharmacy and Chemistry. "Nirvanol." Jr. Am. Med. Assoc., 1933, xcix, 33–34.

170*a*. SCHLESINGER, B.: Case showing effect of nirvanol on subacute rheumatism, Proc. Roy. Soc. Med., 1932, xxv, 717–718. The etiology of acute rheumatism, Brit. Med. Jr., 1933, i, 697–698.

171. SLOT, G.: Discussion, Proc. Roy. Soc. Med., 1932, xxv, 717.

172. FINDLAY, L.: Discussion. Case showing effect of nirvanol on subacute rheumatism, Proc. Roy. Soc. Med., 1932, xxv, 717–718.

173. MURRAY-LYON, R. M.: The treatment of chorea by nirvanol, Edinburgh Med. Jr., 1932, xxxix, 368–375.

174. DENNETT, R. H., and WETCHLER, S.: Nirvanol treatment of acute chorea in children, Jr. Pediatrics, 1932, i, 203–209.

175. WHITAKER, W. M.: Recent developments in treatment of chorea minor, Illinois Med. Jr., 1933, lxiii, 123–129.

176. DENNETT, R. H.: Nirvanol treatment of chorea, Penn. Med. Jr., 1933, xxxvi, 748–751.

177. JONES, T. D., and JACOBS, J. L.: Treatment of obstinate chorea with nirvanol, Jr. Am. Med. Assoc., 1932, xcix, 18–25.

178. WEINFELD, G. F., and COHEN, R.: Nirvanol treatment of chorea, Jr. Pediatrics, 1932, i, 210–215.

179. HERRICK, W. W.: The treatment of rheumatic fever, New York State Jr. Med., 1933, xxxiii, 131–132.

180. ROBEY, W. H.: Tonsillectomy versus medical treatment in cases of rheumatic fever, Med. Clin. N. Am., 1932, xv, 875–885.

181. MILLER, R.: The prevention of rheumatic heart disease, Practitioner, 1933, cxxx, 649–657.

182. FINLAND, M., ROBEY, W. H., and HEIMANN, H.: The effect of tonsillectomy on the occurrence and course of acute polyarthritis: an analysis of 654 consecutive case histories, Am. Heart Jr., 1933, viii, 343–356.

183. WHITTEN, M. B.: Antistreptococcus cardioarthritidis serum and antigen (S.C.A.) in treatment of chronic rheumatic endocarditis; preliminary report, Texas State Jr. Med., 1932, xxviii, 217–223.

184. STROUD, W. D., BROMER, A. W., and GALLAGHER, J. R.: Intravenous vaccine in rheumatic cardiovascular disease, Trans. Assoc. Am. Phys., 1932, xlvii, 29–39.

185. WILSON, M. G., JOSEPHI, M. C., and LANG, D. M.: Intravenous vaccination with streptococci: its influence on the incidence of recurrence of rheumatic fever in children, Am. Jr. Dis. Child., 1933, xlvi, 1329–1337.

186. LEVY, R. L., and GOLDEN, R.: Roentgen therapy of rheumatic heart disease: a review of six years' experience, Am. Jr. Roentgenol. and Radium Therap., 1933, xxix, 79–82.

EDITORIAL

BLOOD FROM THE DEAD FOR TRANSFUSIONS

One of the most perplexing problems to hospitals and to the medical profession is the difficulty of securing blood for transfusions in sufficient quantities at all times and at a cost within the reach of people of limited means who need it.

Under existing conditions the procedure of transfusion is available for use only when the patient is able to pay for a donor, or when a voluntary donor is available, or when the cost can be met from charitable funds. Not infrequently none of these avenues are open and a patient urgently needing transfusion must do without.

To meet this situation scientists in Russia have for some years been studying experimentally in dogs the effects of transfusions in which the blood employed was obtained from a dead canine donor. In 1928 Professor Chaumov of Kharkov reported most favorable results in a considerable number of such canine transfusions.

The experiments were continued at the Moscow Institute of Hematology which has facilities and personnel for clinical, biological, surgical and biochemical procedures, and a laboratory for the manufacture and standardization of serum preparations. Here postgraduate courses are conducted in hematology and noteworthy studies have been conducted since the foundation of the Institute in the anemias, the treatment of various intoxications by transfusion, the perfection of transfusion apparatus and numerous other hematological problems.

It occurred to Professor Sergius Judin, chief surgeon of the Sklifasovski Emergency Hospital in Moscow, after studying the results at Kharkov, that blood from cadavers, if properly tested and aseptically handled, could be utilized for the living, and, since it was impossible for the Institute of Hematology to furnish from living donors the immense quantities of blood required at the Sklifasovski Hospital, Professor Judin collaborated with the Institute in a study of the use of blood from cadavers.

About two years after Professor Chaumov's reports on canine transfusions and after the Hematological Institute had concluded that human experimentation was justifiable, the first use was made of the blood from a cadaver for human transfusion. Under the direction of Professor Judin an engineer brought to the hospital in an exsanguinated, moribund condition due to a self-inflicted wound was transfused with blood from a human cadaver. This case was successful and after repeating the procedure on a series of cases Professor Judin reported the methods used to the Congress of Surgeons of the Ukraine at Kharkov late in 1930. Because of the existence of a statute which prohibited the removal of blood for embalming purposes prior to the completion of an autopsy, it became necessary to gain the ap-

proval of the Surgical Congress to legalize the procedure and so, at this meeting, a resolution was passed certifying to the scientific basis of the procedure, since which time the scope of Professor Judin's actions has been greatly extended and his methods are being used in many other large hospitals in the Soviet Union.

For the recovery of blood from the dead there has been set aside a special pavilion at the Sklifasovski Hospital under the immediate direction of a woman assistant, Dr. Skoundina. This pavilion consists of a number of separate rooms where cadavers are prepared in the same way as for a surgical operation, and an operating room where the cadaver is placed on a table at an enclined plane with a cannula in the jugular vein. The blood is collected in aseptic jars in which there is a solution of sodium citrate; a specimen is sent to the laboratory for a Wassermann and Kahn test, and for culture and typing; the jar of blood, properly identified, is then placed in a refrigerator awaiting the laboratory report on the blood and the report of the pathologist on an autopsy which immediately follows.

If the reports are favorable the type is recorded on the label and the blood is then available for use when needed, it being necessary only to warm it in a water bath to 104° F. before transfusion. If either the laboratory or the autopsy reports indicate any deviation from the normal of the blood or the organs of the body the blood is immediately removed from the refrigerator and discarded.

As a result of a rather extended experience Professor Judin has reached some definite conclusions concerning the procedure which are of universal interest. He prefers the blood obtained from suicides, from those dying of heart disease or from traumatism. In the case of sudden death the blood retains its fluidity longer in the veins and it has been found that in such cases the blood will flow out by gravity after as long as twelve hours. Blood can be preserved without risk for any time up to about twenty-eight days and possibly longer, but Professor Judin prefers blood that is not more than twelve days old, in the belief that as age increases, its potency is affected. There is no preference as to the age or sex of the deceased and blood from an aged individual has given as good results as that from a young athlete. The blood is delivered to the patient by means of gravity through rubber tubing from a heated glass funnel elevated about three feet above the operating table.

The very extensive records available at the Sklifasovski Hospital of over 400 transfusions of the citrated blood from cadavers compared with an equal number of previous transfusions with whole blood lead Professor Judin [1] to the following conclusions:

(*a*) The new method assures an immediate supply of carefully typed, tested and cultured blood from human bodies which have been autopsied and found free from organic disease.

[1] JUDIN, SERGIUS: La transfusion du sang de cadavre à l'homme, Paris, 1933.

(*b*) There are fewer unfavorable reactions from the refrigerated supply than from the blood of living donors.

(*c*) Because a sufficient supply of blood is always available at little cost, there need be no hesitancy in resorting to transfusion whenever indicated and a considerable number of lives has been saved, not to mention the more rapid convalescence of many grave surgical cases.

(*d*) Transfusion is placed within the reach of all of the people and while the extraction and storage of blood from cadavers can only be conducted by large institutions, the blood can be transported by airplane or otherwise under proper conditions to any distant point and in any quantity.

WILLIAM H. WALSH

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.: David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume VII: Pediatrics.* Associate Editor DANIEL C. DARROW, B.A., M.D., Assistant Professor of Pediatrics, Yale University Medical School. xxxvi + 1211 pages, 92 illustrations. D. Appleton-Century Company, New York. 1935. Price, $10.00 a volume.

The preceding six volumes of *The Practitioner's Library of Medicine and Surgery,* presenting respectively Anatomy and Physiology as Applied to Practical Medicine, The Technic of Physical and Laboratory Examination in Clinical Medicine, Practice of Medicine, Nontraumatic Surgery, Traumatic Surgery and Gynecology and Obstetrics, have been reviewed in THE ANNALS as they have appeared. When complete the Library will total 12 subject volumes and a combined Supplement-Index.

To Volume VII, *Pediatrics,* there are 34 contributors who have been chosen because of their knowledge and comprehension of the problems of the general practitioner in the field of the diseases of infancy and childhood. The choice of chapter headings and the proportion of space allotted to each topic give further evidence of thoughtful regard for the needs of that large group for whom this work is planned. As has been mentioned in reviewing the preceding volumes, the unusual, rare or controversial condition cannot be treated in an exhaustive manner in such a book. Rather must the emphasis be placed upon those groups of affections with the prevention and treatment of which troublesome questions frequently arise. Thus among the thirty-four chapters we find special attention is given to defective nutrition, diseases of the gastrointestinal tract, and the infections of childhood. The chapters on diarrheal diseases of infants, diseases of the upper respiratory tract, pneumonia and tuberculosis are especially to be commended. Less serious affections of frequent occurrence also are well treated as, for instance, enuresis, which is discussed in six pages abounding in good common sense. Much less satisfactory is the discussion of diseases of the thymus which gives but slight implication of the constitutional significance of thymic hyperplasia. In this connection it should be noted that 'thymus' can be found in the index only under 'gland.' The final index volume will doubtless include a more comprehensive listing. In style and execution this volume maintains the high standards of the series. It will prove a very useful addition to the library of the practitioner.

C. V. W.

Human Personality and the Environment. By C. MACFIE CAMPBELL, M.D. 252 pages; 15 × 22 cm. Macmillan Co., New York. 1934. Price, $3.00.

"This book presents the substance of six lectures delivered before a lay audience at the Lowell Institute, Boston, in February, 1933."

Dr. Campbell, one of America's outstanding psychiatrists, develops the theme of the personality as an integrated biological unit reacting to the whole environment. He begins with its responses to the physico-chemical factors as represented by foods, climate and atmospheric changes; turns to the rôles played by the component parts of the organism—the endocrines, the vegetative and central nervous systems and their influences upon the personality; then swings to the individual's development from its earliest beginnings as an individual to its mature organization as a more or less stable adult, meeting life-situations both within and without.

The part played by unconscious factors, the persistence of primitive and childhood views, find their place in the adult. Individual variations are pointed out. The text is illustrated by references to the lives of artists, scientists, philosophers and men of letters, notably Darwin, Beethoven and Schopenhauer.

This is a well written book, and one which is important to anyone who has any interest in the patient as a person, not as a vehicle for pathology.

H. M. M.

Murrell's *What to Do in Cases of Poisoning.* By P. HAMILL, M.D., D.Sc., F.R.C.P., Lecturer on Pharmacology and Therapeutics, St. Bartholomew's Hospital Medical College; Senior Physician to the Metropolitan Hospital. 208 pages; 10.5 × 16.5 cm. Paul B. Hoeber, Inc., New York. 1934. Price, $1.50.

This pocket-sized manual represents the fourteenth edition of a treatise on poisoning which was first published by the late Dr. W. Murrell in 1881 and which has been carried on by Dr. Hamill since 1921. To facilitate reference the book has been completely reset in larger type and page.

The initial sections on Classification, Antidotes, Emetics, etc., and especially on Diagnosis of Poisoning, are excellent in their terse but adequate presentation. The body of the volume comprises a discussion first of acute, then of chronic poisonings, arranged in alphabetical order. It includes symptoms, fatal dose and treatment. The index is satisfying in its completeness.

While it is understood that brevity must be the very soul of such a treatise, many will feel that in certain instances the author has over-reached himself in this respect. Thus, no mention is made of the efficacy of calcium in quieting the acute phases of lead poisoning; there is no allusion to the use of methylene blue intravenously in cyanide poisoning; the forcing of large quantities of fluids in acute mercurial poisoning is not mentioned—a point now being universally stressed; the treatment given for methyl alcohol poisoning is inadequate. No mention is made of the possible severe acidosis or of increased spinal fluid pressure—the appropriate treatment of which may save the patient's sight or life.

There is a real need for a volume of this size and price and if it can manage to be concise, yet at the same time sufficiently inclusive and up to the times, it will undoubtedly enjoy wide popularity.

H. R. P.

A Text-Book of Pathology. By WILLIAM BOYD, M.D., M.R.C.P., F.R.C.P., Professor of Pathology in the University of Manitoba. Second edition. 1047 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1934. Price, $10.00.

This book represents the revision of a first edition which appeared in 1932. The division of the book into two parts, viz: General Pathology and Special Pathology, is retained. The subject matter under general pathology is presented in a more logical order than is usual so that the reader, particularly the student, is made acquainted with the important facts concerning disorders of metabolism and local disturbances in the circulation as an introduction to the study of inflammation and repair.

New material has been added to the text, notably on the subjects of Von Gierke's glycogen storage disease, lead poisoning in children, medionecrosis of the aorta in its relation to dissecting aneurysm, renal architecture in chronic nephritis and recent studies of encephalitis.

Although a considerable number of new illustrations is presented, future editions might be improved by further additions, especially in the matter of tumors.

References for additional reading have been extended and they are, for the most part, well chosen. Since the book covers rather thoroughly the common as well as

the more unusual diseases, the brief discussions of certain subjects apparently represent an effort on the part of the author to keep the book within the limits of a single volume.

H. R. S.

Clinical Pathology of the Jaws. By KURT H. THOMA, D.M.D., Boston, Mass. 643 pages; 17 × 25.5 cm. Charles C. Thomas, Baltimore. 1934. Price, $9.00.

In this day of increasing interest in cancer and allied diseases, any book amplifying our knowledge by condensing masses of accumulated data is a welcome adjunct to medical literature. This is especially true in the understudied field of oral surgery—the "No Man's Land of the human body"—as the author terms it. Although there are many developmental abnormalities of the jaws as well as infections, injuries, fractures, endocrine and nutritional disturbances, nevertheless tumors of the jaws, benign and malignant, take a huge toll in the number of oral cases seen in clinic and private practice. Chronic inflammation from badly kept teeth, dental caries and tobacco, add to the neoplasms of congenital origin to increase the high percentage of mouth malignancies. This the author emphasizes by devoting 481 pages to neoplasms and like lesions, out of a total of 629 pages of text. Sufficient space, however, is given to congenital abnormalities, infections, fractures and other diseases.

The book is bound in dark blue cloth binding and printed on good glazed paper with moderately easy reading type. There are 423 illustrations including photographs of patients, roentgenograms and numerous photomicrographs, some in colors. The free use of photomicrographs is of great value—an adjunct frequently overlooked in many texts. Unfortunately there is no list of illustrations.

The author "treats of physical, roentgen, and microscopic examination, applying the findings to diagnosis and treatment," correlating data gleaned from a large number of sources including 12 hospitals and dispensaries in America and one in Europe. The repeated use of case histories, especially since these histories are indexed in the back of the book for practical illustration, is helpful. At the end of each chapter there is an ample bibliography.

A short but useful appendix of routine laboratory stains and a general index are given.

In order to make available, at a low cost, a book so extensively illustrated, especially one with so many photomicrographs, a grant was obtained from the Milton Fund of Harvard University.

G. E. W.

Wish Hunting in the Unconscious. By MILTON HARRINGTON, M.D. 189 pages; 13.5 × 19.5 cm. Macmillan Company, New York. 1934. Price, $2.50.

"Most of us are too busy taking care of our own personal affairs or advancing some cause with which we are identified to spare much time on the thankless task of trying to pull down other people's houses."

Dr. Harrington feels that psycho-analysis is a structure which should be razed, and his own erected in its place. He does not believe that behavior is a response to emotional demands, but is "made up of two different kinds of action: (1) Movements or changes of position, which are produced by the muscles, and (2) chemical changes, which are produced by the glands." He considers analysis a form of suggestion which sees in each problem exactly what the analyst is looking for, and in which the patient is inclined to give up his symptoms and accept an explanation for them, whether or not that explanation is true, because of the patient's love for the analyst. Resistance is only a convenient way of avoiding explanations which the analyst is unwilling to give or which interfere with his views. Breaking it down is breaking down the patient's critical judgment and common sense. In accepting thoughts or

fantasies as valid items of experience, the analyst manufactures evidence to support his theory. Analysis itself is a species of religious conversion, blinding its devotees to truth. Its popular success is based partly upon the strength of this, partly because it explains everything and partly because it "includes a thrilling sexual experience thrown in." In short it is an "expensive long drawn-out course of muck raking for pervert sexual desires in the cesspool of the unconscious."

The antagonism apparent throughout leads one to discredit its validity as a critical work. The author's own alternative theory is unsatisfactory. No evidence is brought forth to support his views.

H. M. M.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the College have become Life Members by contributing the specified fees to the Endowment Fund of the American College of Physicians:

Dr. Joseph M. King, Los Angeles, Calif.....January 21, 1935
Dr. Wm. J. Stapleton, Jr., Detroit, Mich.....January 21, 1935
Dr. George E. Baxter, Chicago, Ill.....January 22, 1935
Dr. Clifford E. Henry, Minneapolis, Minn.....March 8, 1935

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Wilburt C. Davison (Fellow), Durham, N. C.—one book, "The Compleat Pediatrician";
Dr. Ralph O. Clock (Fellow), New York, N. Y.—one reprint;
Dr. Harold Swanberg (Fellow), Quincy, Ill.—four reprints;
Dr. Frederick R. Taylor (Fellow), High Point, N. C.—two reprints;
Dr. Felix J. Underwood (Fellow), Jackson, Miss.—one reprint;
Dr. S. Arthur Weisman (Fellow), Minneapolis, Minn.—nine reprints;
Dr. Ralph M. Fellows (Associate), Topeka, Kansas—one reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Rafael Rodriguez-Molina (Associate), San Juan, P. R.—six reprints;
Dr. P. H. Sprague (Associate), Edmonton, Alberta, Can.—one reprint.

A Round Table Clinic Day was held by the Fellows and Associates of the American College of Physicians residing in western Pennsylvania, and surrounding country, at the Falk Clinic on February 22, 1935. The members were called together by Dr. E. Bosworth McCready, Governor of the College for western Pennsylvania, and the program was arranged by Dr. Joseph H. Barach, Dr. John M. Thorne and Dr. Clement R. Jones, Chairman, all of Pittsburgh. Members were present not only from the western Pennsylvania towns, but from Wheeling, Fairmont and Youngstown.

Dr. Joseph H. Barach gave a clinic on diabetes, Dr. Clement R. Jones a clinic on syphilis of the stomach, and members of the Falk Clinic staff gave additional clinics on peptic ulcer and migraine. The discussions were general and interesting. The group voted to suggest that such a meeting be held twice a year in the future.

Dr. W. R. Houston (Fellow and Governor of the College for the State of Georgia) has removed from Augusta and established practice in Austin, Texas.

Dr. William Gerry Morgan (Fellow) and Dr. Hugh S. Cumming (Fellow) addressed a special public meeting of the District of Columbia Tuberculosis Association, Washington, D. C., on March 30, 1935, on "Modern Medical and Surgical Treatment" and "Coördinating Public and Private Health Agencies to Control Tuberculosis," respectively.

Dr. George Adams Merrill (Fellow), Brooklyn, N. Y., was recently elected Director of Medicine and President of the Medical Board of the Kings County Hospital. He is also President of the Brooklyn Society of Internal Medicine for the present year.

Dr. C. Walter Clarke (Fellow) has been appointed by the Office of Indian Affairs, United States Department of the Interior, a Special Consultant on Syphilis. Dr. Clarke is conducting a series of lecture demonstrations for the medical personnel of the Indian Service and will initiate epidemiological studies of syphilis among the Indians.

Dr. Conrad Wesselhoeft (Fellow), Associate in Communicable Diseases at Harvard Medical School, has received from the War Department the Oak Leaf Cluster for extraordinary heroism in establishing and operating a first-aid station near the front line trenches, under intense machine gun and artillery fire, from July 18 to 28, 1918. Dr. Wesselhoeft went overseas with the 26th Division, and was promoted to Captain. He served in the following engagements: Chemin des Dames sector, La Reine sector, Chateau-Thierry, Saint-Mihiel, and Meuse-Argonne offences, and received the Distinguished Service Cross and the Croix de Guerre and was twice cited in general orders, Headquarters, 26th Division.—*Harvard Alumni Bulletin, February 8, 1935.*

Dr. Lyell C. Kinney (Fellow), San Diego, Calif., is a Vice-President of the American Roentgen-Ray Society for the present year.

Dr. David Riesman (Fellow), Philadelphia, Pa., is President-Elect of the Interstate Postgraduate Medical Association.

Dr. Edward B. Vedder (Fellow), Washington, D. C., is the President of the American Society of Tropical Medicine.

Dr. Jacob C. Geiger (Fellow), Health Officer of San Francisco, is President of the San Francisco County Medical Society.

Dr. Clarence E. Simonds (Fellow), Willimantic, Conn., has been appointed Health Officer of Windham, Conn.

Dr. John A. Kolmer (Fellow) has been placed in charge of a new department for research on bacteriophage at Temple University Hospital, Philadelphia.

Dr. Lewellys F. Barker (Fellow), Baltimore, Md., delivered the Beaumont Lectures of the Wayne County Medical Society, Detroit, Mich., February 4 to 5 on "Heredity and Environment in Relation to the Handicapped." Dr. Barker also addressed the Wayne University Medical School students, February 5, on "Major and Minor Medical Morals."

The University of Michigan has recently established a division of health sciences as an advisory unit of the institution. It will include the Medical School, School of Dentistry, Division of Hygiene and Public Health, School of Nursing, College of Pharmacy and the Department of Postgraduate Medicine. Dr. James D. Bruce (Fellow and Governor), who is Vice-President of the University and Head of the Department of Postgraduate Medicine, has been named Chairman of the newly created division.

Dr. Carl V. Weller (Fellow), Professor of Pathology, and Dr. Udo J. Wile (Fellow), Professor of Dermatology, have been named members of an Executive Committee for the division.

Dr. James Burns Amberson, Jr. (Fellow) has recently been appointed Assistant Professor of Clinical Medicine at the New York University and Bellevue Hospital Medical College.

Dr. Charles James Bloom (Fellow), New Orleans, read before the Southern Medical Association in San Antonio on November 16, 1934, a paper entitled "Thyrotoxicosis in Children."

OBITUARIES

EDGAR MOORE GREEN

Dr. Edgar Moore Green (Fellow), born in September 1862, died March 9, 1935. He was a son of the late Dr. Traill Green and Harriet Moore Green. On his maternal side he was a descendant in the eighth generation of John and Priscilla Mullins Alden. He received his early education in public and private schools, graduating from Easton High School in 1879. He entered Lafayette College where he was one of the Junior orators, won the mathematical, astronomical and Early English Text Society's prizes and was graduated in the class of 1883, delivering the honorary oration in astronomy. He received his medical degree in 1886 from the University of Pennsylvania, being awarded the prize for the highest average. From 1895 to 1897 he was pathologist to St. Luke's Hospital, Bethlehem, Pa. He was a member of the Board of Trustees of Lafayette College. From 1904 to 1924 he was Physician-in-Chief to the Easton Hospital. He was consulting internist to St. Luke's Hospital, Bethlehem; Norristown State Hospital, and Warren Hospital, Phillipsburg, N. J. He was a member of the Advisory Board of the State Department of Health and also a member of the State Board of Medical Education and Licensure. He held membership in the Phi Kappa Psi, Alpha Mu Pi Omega, and Phi Beta Kappa fraternities. He was a member of the Northampton County Medical Society, the Medical Society of the State of Pennsylvania, the American Medical Association, and the Philadelphia Pathological Society. In 1917 he received the honorary degree of Doctor of Science from Pennsylvania College at Gettysburg, Pa. In 1924 he became a Fellow of the American College of Physicians.

Had Dr. Green lived but ten days longer he would have seen the completion of a century of continuous service rendered by his father and himself in the field of medicine in Easton. He was uniformly courteous and kindly. He was beloved by all who knew him. His passing leaves a gap which will be difficult to fill.

FRANCIS J. DEVER, M.D., F.A.C.P.

STEPHEN LIVINGSTON TAYLOR

Dr. Stephen Livingston Taylor, Associate of the American College of Physicians since 1925, died in the Faulkner Hospital, Boston, Massachusetts, of heart disease, January 29, 1935, aged 66 years.

Dr. Taylor was a graduate of Amherst College and received his medical degree from the College of Physicians and Surgeons of Columbia University in 1894. He pursued postgraduate study at the Trudeau School of Tuberculosis. From 1904 to 1914 he was attending physician to the Brooklyn Orphans' Asylum; from 1906 to 1912, assistant surgeon to the Methodist Episcopal Hospital; and for many years, attending physician to the Broad Street Hospital of Oneida, N. Y. Dr. Taylor was also the health officer of Sherrill for a long period of years. He was a member of his county and state medical societies, of the National Tuberculosis Association, and a Fellow of the American Medical Association.

JAMES EDWIN CAMPBELL TAYLOR

Dr. James Edwin Campbell Taylor (Associate), Columbus, Ohio, died December 12, 1934, of influenza, aged 35 years.

Dr. Taylor was born at Columbus, Ohio, December 5, 1899. He held the degrees of A.B. (1921) from Harvard University and Doctor of Medicine (1928) from the Ohio State University College of Medicine. He was medical intern at the Kings County Hospital, Brooklyn, N. Y., for one and one-half years and concluded a two-year medical Fellowship at the Mayo Clinic. Afterwards, he became Assistant in the Ohio State University College of Medicine. He was a member of the Attending Staff of Mt. Carmel and St. Francis Hospitals and a member of the Visiting Staff of the White Cross and University Hospitals. He was elected an Associate of the American College of Physicians during 1932.

HARRY SAMUEL WAGNER

Dr. Harry Samuel Wagner (Fellow), Pocasset, Massachusetts, died February 8, 1935, in the Baker Memorial Hospital, Boston, aged 57 years.

Dr. Wagner was born in Toledo, Ohio, June 4, 1877. He received the degree of Ph. B. from Denison University in 1899 and the degree of Doctor of Medicine from the University of Michigan Medical School in 1903. He was Assistant Superintendent of the Westfield State Sanatorium from 1910 to 1912; Superintendent of the Hartford State Sanatorium from 1912 to 1916; Superintendent of the Pressmen's Sanatorium from 1916 to 1919; and had been Superintendent of the Barnstable County Sanatorium, Pocasset, Massachusetts, since 1919.

Dr. Wagner was a member of the Barnstable County Medical Society, Massachusetts Medical Society, National Tuberculosis Association, American Sanatorium Association, Trudeau Society of Boston, and a Fellow of the American Medical Association. Dr. Wagner became a Fellow of the American College of Physicians during 1929.

HIRAM DAVIS LAWHEAD

Dr. Hiram Davis Lawhead (Associate), Woodland, California, died November 29, 1934, of coronary occlusion, aged 82 years.

Dr. Lawhead was indeed a distinguished member of his community, and his deeds of goodness to the people and his support of cultural activities for the community were outstanding. He was a school teacher for a number of years, then studied medicine at Cooper Medical College, San Francisco, graduating in 1883. He began practice at Knights Landing; but in 1887 located at Woodland, and practiced there continuously for forty-seven years.

Dr. Lawhead contributed several worthwhile articles to the medical literature, more especially one upon the "Art of Medicine" in 1926. He was a charter member of his local county medical society, the Yolo-Colusa-Glenn Society for Medical Improvement, and served as president, as well as secretary, for several years. He was likewise a charter member and president for one year of the Northern District Medical Association of California, a member of the California Medical Association, and a member of the American Medical Association. He became an Associate of the American College of Physicians in 1922.